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Nexium®
(esomeprazole magnesium)

20-MG. 40-MG Delayed-Release Capsules

BRIEF SUMMARY Before prescribing NEXIUM, please see full Prescribing Information **INDICATIONS AND USAGE** NEXIUM is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. **CONTRAINDICATIONS** NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles. **PRECAUTIONS** Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer. **Information for Patients:** NEXIUM Delayed-Release Capsules should be taken at least one hour before meals. For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the capsule opened, and the pellets carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use. Antacids may be used while taking NEXIUM. **DRUG INTERACTIONS** Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole-metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance. Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole. Esomeprazole inhibits gastric acid secretion, therefore, it is theoretically possible that esomeprazole and omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg. ketoconazole, ampicillin esters, digoxin, and iron salts). **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals. **Pregnancy:** *Teratogenic Effects. Pregnancy Category B* - Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. **Nursing Mothers:** The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole and omeprazole are likely to be excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from esomeprazole and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of patients who received NEXIUM in clinical trials, 778 were 65 to 74 years of age and 124 patients were ≥ 75 years of age. No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,400 patients in the United States and over 2,600 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short- and long-term clinical trials. The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole. Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system: ***Body as a Whole:*** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; ***Cardiovascular:*** flushing, hypertension, tachycardia; ***Endocrine:*** goiter; ***Gastrointestinal:*** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms NOS, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; ***Hearing:*** earache, tinnitus; ***Hematologic:*** anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; ***Hepatic:*** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic/Nutritional:*** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; ***Musculoskeletal:*** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; ***Nervous System/Psychiatric:*** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; ***Reproductive:*** dysmenorrhea, menstrual disorder, vaginitis; ***Respiratory:*** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages:*** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; ***Special Senses:*** otitis media, parosmia, taste loss, taste perversion; ***Urogenital:*** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; ***Visual:*** conjunctivitis, vision abnormal. Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration. Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert. **OVERDOSAGE** A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. There have been no reports of overdose with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert-**ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

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PRiLOSEC®
(OMEPRAZOLE)

20-MG Delayed-Release Capsules

BRIEF SUMMARY Before prescribing PRILOSEC, please see full Prescribing Information. **INDICATIONS AND USAGE** *Erosive Esophagitis:* PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) in the healing of erosive esophagitis, which has been diagnosed by endoscopy. **CONTRAINDICATIONS Omeprazole** PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation. **PRECAUTIONS** Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole. **Information for Patients:** PRILOSEC Delayed-Release Capsules should be taken before eating and should not be opened, chewed or crushed, and should be swallowed whole. **DRUG INTERACTIONS** *Other* Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg. cyclosporine, disulfiram, and benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC. Omeprazole inhibits gastric acid secretion, therefore, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg. ketoconazole, ampicillin esters, digoxin, and iron salts). In clinical trials, antacids were used concomitantly with the administration of PRILOSEC. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative. In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals. **Pregnancy:** *Category C* - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRILOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole and 120 patients took a placebo. A causal relationship was not assessed. The percentages are given omeprazole then placebo, respectively. *Body as a Whole, site unspecified:* Abdominal Pain 5.2% and 3.3%; Asthenia 1.3% and 0.8%. *Digestive System.* Constipation 1.5 and 0.8; Diarrhea 3.7 and 2.5; Flatulence 2.7 and 5.8; Nausea 4.0 and 6.7; Vomiting 3.2 and 10.0; Acid regurgitation 1.9 and 3.3; *Nervous System/Psychiatric:* Headache 2.9 and 2.5. Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRILOSEC was unclear. *Body As a Whole:* Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling. *Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema. *Gastrointestinal:* Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors. *Hepatic:* Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy. *Metabolic/Nutritional:* Hyponatremia, hypoglycemia, weight gain. *Musculoskeletal:* Muscle cramps, myalgia, muscle weakness, joint pain, leg pain. *Nervous System/Psychiatric:* Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia. *Respiratory:* Epistaxis, pharyngeal pain. *Skin:* Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis. *Special Senses:* Tinnitus, taste perversion. *Urogenital:* Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia. *Hematologic:* Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

OVERDOSAGE Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16-45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

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Reference: 1. Prescribing Information for NEXIUM.

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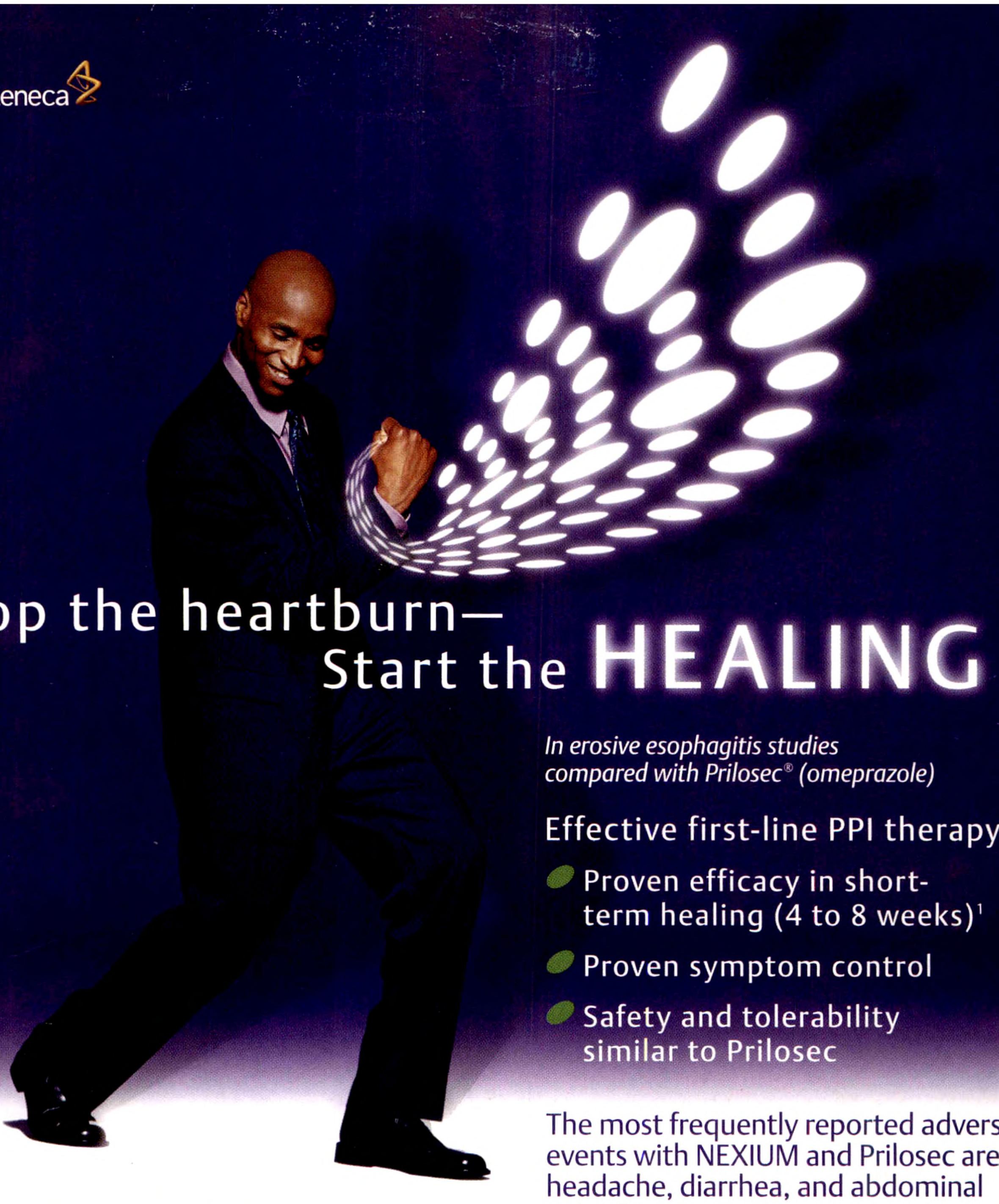

Stop the heartburn—
Start the HEALING

In erosive esophagitis studies compared with Prilosec® (omeprazole)

Effective first-line PPI therapy:

- Proven efficacy in short-term healing (4 to 8 weeks)[1]
- Proven symptom control
- Safety and tolerability similar to Prilosec

The most frequently reported adverse events with NEXIUM and Prilosec are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy.

P24750

NEXIUM and Prilosec should be used only for the conditions, dosages, and durations specified in the Prescribing Information. Before prescribing NEXIUM or Prilosec, please see brief summary of full Prescribing Information on next page.

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Please visit our web site at www.nexium-us.com

Nexium®
(esomeprazole magnesium)
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Q:

What does a hematologist in Chicago have in common with an internist in San Francisco and a rheumatologist in Philadelphia?

A:

They all made the connection.

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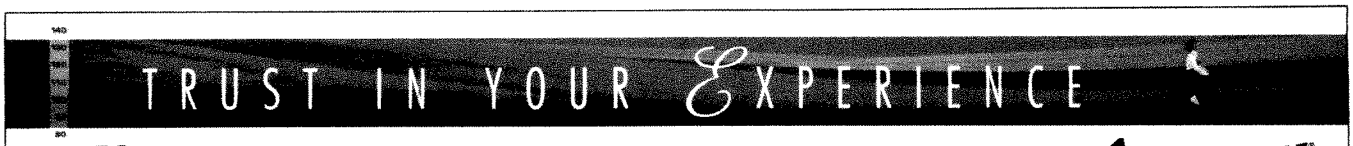

10 years of clinical experience **6.5 billion patient-days of therapy**

Over 15,000 patients in open-label clinical trials

Accupril®
quinapril HCl tablets
ENTER THE CONTROL ZONE™

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

BRIEF SUMMARY: Consult Package Insert for full prescribing information.

INDICATIONS AND USAGE: Hypertension: ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics. **Heart Failure:** ACCUPRIL is indicated in the management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

Angioedema in black patients: Black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to nonblacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks.

CONTRAINDICATIONS: ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS: Anaphylactoid and Possibly Related Reactions: Presumably because angiotensin-converting inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ACCUPRIL) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. In two similarly sized U.S. postmarketing trials that, combined, enrolled over 3,000 black patients and over 19,000 nonblacks, angioedema was reported in 0.30% and 0.55% of blacks (in studies 1 and 2, respectively) and 0.39% and 0.17% of nonblacks.

Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Patients with a history of angioedema: Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hepatic Failure: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hypotension: Excessive hypotension is rare in patients with uncomplicated hypertension treated with ACCUPRIL alone. Patients with heart failure given ACCUPRIL commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy in patients with heart failure (see DOSAGE AND ADMINISTRATION in full prescribing information). In controlled studies, syncope was observed in 0.4% of patients (N=3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include patients with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or cautiously increase salt intake (except in patients with heart failure) before initiating therapy with ACCUPRIL in patients at risk for excessive hypotension who are able to tolerate such adjustments.

In patients at risk of excessive hypotension, therapy with ACCUPRIL should be started under close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ACCUPRIL and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of ACCUPRIL, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of ACCUPRIL or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

PRECAUTIONS: General: Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function (see DOSAGE AND ADMINISTRATION in full prescribing information).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION in full prescribing information).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on an mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on an mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy: Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Because ACCUPRIL is secreted in human milk, caution should be exercised when this drug is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of ACCUPRIL in pediatric patients have not been established.

Geriatric Use: Clinical studies of ACCUPRIL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of the toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients exhibited increased area under the plasma concentration time curve and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself.

ADVERSE REACTIONS: Hypertension: ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 4.7% of patients with hypertension.

Percentages of adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL were headache (Incidence 5.6, Discontinuance 0.7), dizziness (3.9, 0.8), fatigue (2.6, 0.3), coughing (2.0, 0.5), nausea and/or vomiting (1.4, 0.3), abdominal pain (1.0, 0.2).

Similar rates of adverse experiences in the 579 patients who were treated with placebo were headache (10.9, 0.7), dizziness (2.6, 0.2), fatigue (1.0, no discontinuance), coughing (0.0, no discontinuance), nausea and/or vomiting (1.9, 0.2), abdominal pain (0.7, no discontinuance).

Heart Failure: ACCUPRIL has been evaluated for safety in 1222 ACCUPRIL-treated patients. Of these, 632 patients participated in controlled clinical trials. In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 6.8% of patients with congestive heart failure.

Percentages of adverse experiences probably or possibly related or of unknown relationship to therapy occurring in 1% or more of the 585 patients in placebo-controlled congestive heart failure trials who were treated with ACCUPRIL were dizziness (Incidence 7.7, Discontinuance 0.7), coughing (4.3, 0.3), fatigue (2.6, 0.2), nausea and/or vomiting (2.4, 0.2), chest pain (2.4, no discontinuance), hypotension (2.9, 0.5), dyspnea (1.9, 0.2), diarrhea (1.7, no discontinuance), headache (1.7, no discontinuance), myalgia (1.5, no discontinuance), rash (1.4, 0.2), back pain (1.2, no discontinuance).

Similar rates of adverse experiences in the 295 patients who were treated with placebo were dizziness (Incidence 75.1, Discontinuance 1.0), coughing (1.4, no discontinuance), fatigue (1.4, no discontinuance), nausea and/or vomiting (0.7, no discontinuance), chest pain (1.0, no discontinuance), hypotension (1.0, no discontinuance), dyspnea (2.0, no discontinuance), diarrhea (1.0, no discontinuance), headache (1.7, 0.3), myalgia (2.0, no discontinuance), rash (1.0, no discontinuance), back pain (0.3, no discontinuance).

See PRECAUTIONS, Cough.

Hypertension and/or Heart Failure: Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5% to 1.0% (except as noted) of the patients with CHF or hypertension treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N=4847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise, viral infections. **Cardiovascular:** palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances, cardiogenic shock.* **Hematology:** *hemolytic anemia.* **Gastrointestinal:** flatulence, dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests.* **Nervous/Psychiatric:** somnolence, vertigo, syncope, nervousness, depression, insomnia, paresthesia. **Integumentary:** alopecia, increased sweating, pemphigus, pruritus, *exfoliative dermatitis, photosensitivity reaction, dermatopolymyositis.* **Urogenital:** urinary tract infection, impotence, *acute renal failure, worsening renal failure.* **Respiratory:** *eosinophilic pneumonitis.* **Other:** amblyopia, edema, arthralgia, pharyngitis, *agranulocytosis, hepatitis, thrombocytopenia.*

Fetal/Neonatal Morbidity and Mortality

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: Angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings: Hematology: (See WARNINGS).

Hyperkalemia: (See PRECAUTIONS).

Creatinine and Blood Urea Nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of all patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy. In controlled studies of heart failure, increases in blood urea nitrogen and serum creatinine were observed in 11% and 8%, respectively, of patients treated with ACCUPRIL; most often these patients were receiving diuretics with or without digitalis.

OVERDOSAGE: No data are available with respect to overdosage in humans. Doses of 1440 to 4280 mg/kg of quinapril cause significant lethality in mice and rats.

The most likely clinical manifestation would be symptoms attributable to severe hypotension.

Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose. No data are available to suggest physiological maneuvers (eg, maneuvers to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of quinapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat quinapril overdose by infusion of normal saline solution.

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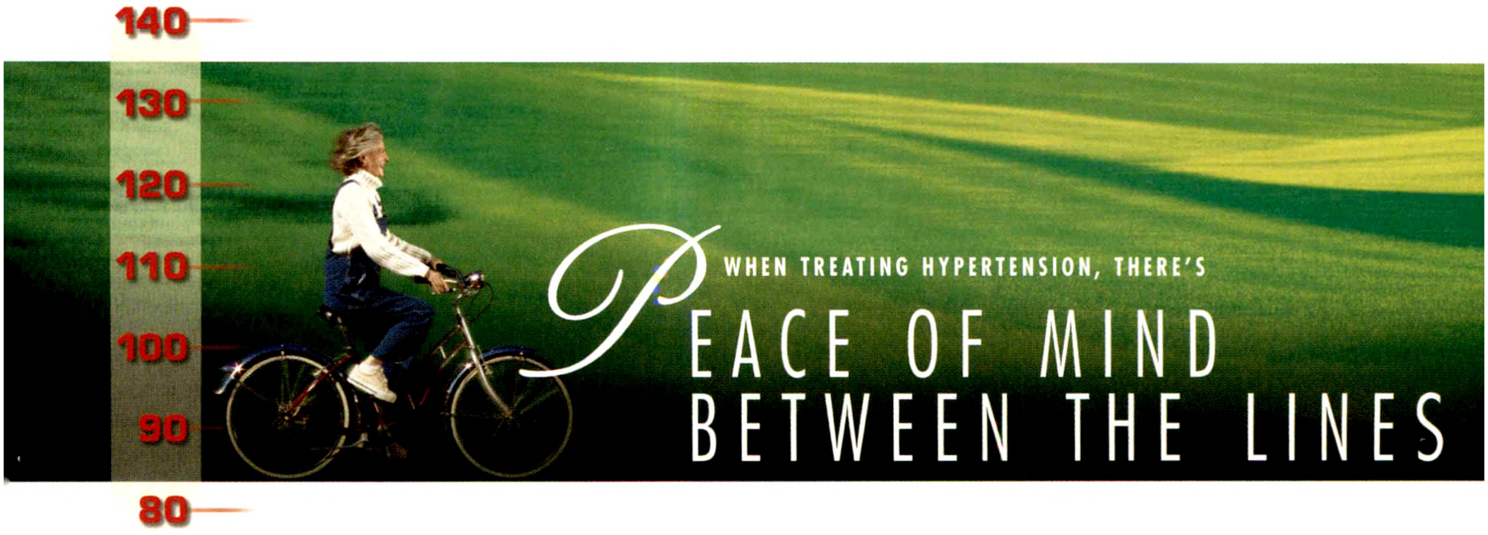

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Mean BP at baseline		Mean BP at visit 3		Mean BP reduction
152/95 mm Hg	**-**	**134/83** mm Hg	**=**	(SBP) **-18** mm Hg (DBP) **-12** mm Hg

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The ATIME study was a randomized, parallel-group, open-label study in 2935 patients with mild hypertension. In the study arm cited (n=1208), therapy was initiated at 20 mg qd and doubled every 6 weeks (3 visits total) until a BP of <140/90 mm Hg or a dose of 80 mg was reached. The mean dose at end of study was 35 mg.

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ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Angioedema has been reported with ACE inhibitors, including ACCUPRIL.

In clinical trials for hypertension with ACCUPRIL, the most common adverse events were headache (5.6%), dizziness (3.9%), fatigue (2.6%), and coughing (2.0%).

In multiple-dose studies, 10-80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5-11/3-7 mm Hg, representing about 50% of the peak effect.

ACE inhibitors should not be used in pregnancy.

Please see brief summary of full prescribing information on adjacent page.

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Empirical therapy with an aminoglycoside and a β-lactam remains common for febrile neutropenic patients. Concerns about aminoglycoside-induced ototoxicity and nephrotoxicity have led to studies of alternate regimens. In this study, ciprofloxacin–piperacillin was as safe and effective as tobramycin–piperacillin for empirical therapy of neutropenic fever.

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In patients with moderate to severe histoplasmosis associated with AIDS, the preferred treatment has been the deoxycholate formulation of amphotericin B. However, serious side effects are associated with this drug. This study found that liposomal amphotericin B was less toxic than amphotericin B and was associated with improved survival.

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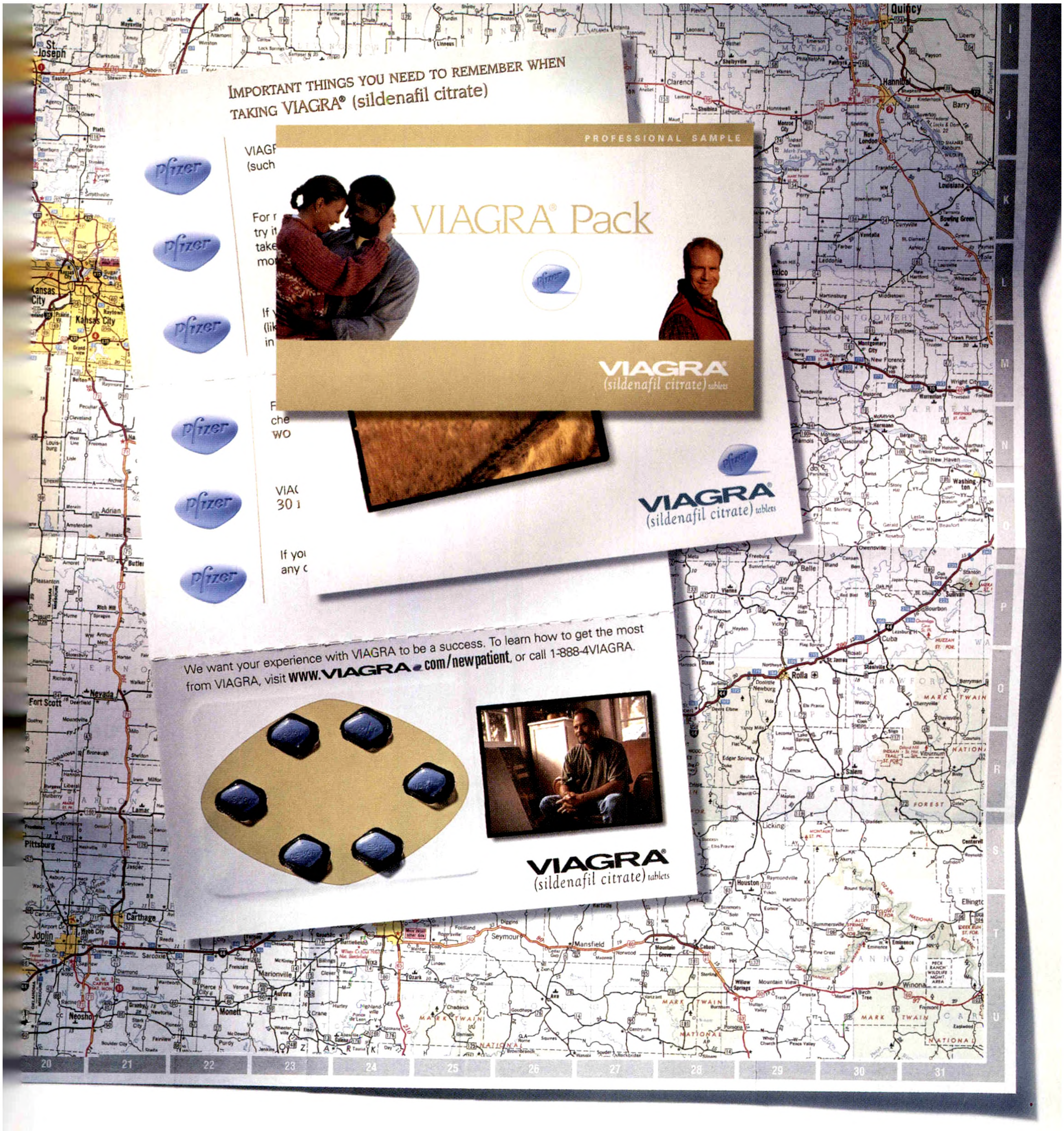
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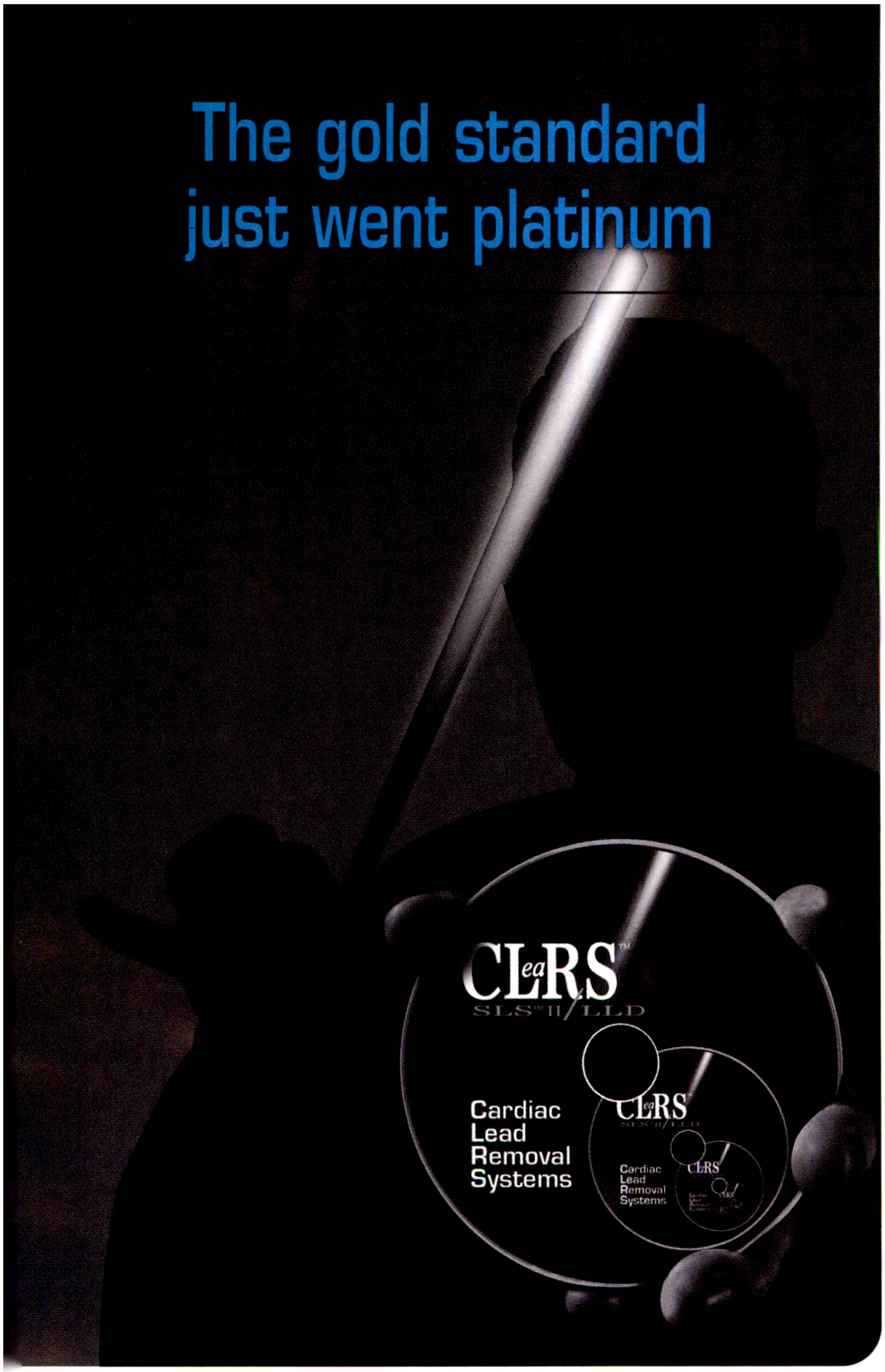

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Böhm, Á., et al: Complications Due to Abandoned Noninfected Pacemaker Leads: PACE: 24:1721-1724, December 2001

Kennergren, C., et al: Cardiac Lead Extraction with a Novel Locking Stylet: Journal of Interventional Cardiac Electrophysiology: 4:591-593, December 2000

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Brief Summary of Prescribing Information

(Nos. 1541, 3046, 7309, 7311)
03-5133-R17-Brf.-Rev. September, 2001

PREVACID®
(lansoprazole)
Delayed-Release Capsules

PREVACID®
(lansoprazole)
For Delayed-Release Oral Suspension

Rx only

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are indicated for:

1. Short-Term Treatment of Active Duodenal Ulcer
2. *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
   - Triple Therapy: PREVACID/amoxicillin/clarithromycin
   - Dual Therapy: PREVACID/amoxicillin
3. Maintenance of Healed Duodenal Ulcers
4. Short-Term Treatment of Active Benign Gastric Ulcer
5. Healing of NSAID-Associated Gastric Ulcer
6. Risk Reduction of NSAID-Associated Gastric Ulcer
7. Gastroesophageal Reflux Disease (GERD)
   - Short-Term Treatment of Symptomatic GERD
   - Short-Term Treatment of Erosive Esophagitis
8. Maintenance of Healing of Erosive Esophagitis
9. Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

CONTRAINDICATIONS

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are contraindicated in patients with known hypersensitivity to any component of the formulations.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin before prescribing.)

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic, and in patients receiving terfenadine therapy who have preexisting cardiac abnormalities or electrolyte disturbances. (Please refer to full prescribing information for clarithromycin before prescribing.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (SEE **WARNINGS** IN PRESCRIBING INFORMATION FOR CLARITHROMYCIN.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients

PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension should be taken before eating.

Alternative Administration Options

PREVACID Delayed-Release Capsules

For patients who have difficulty swallowing capsules, PREVACID Delayed-Release Capsules can be opened, and the intact granules contained within can be sprinkled on one tablespoon of either applesauce, ENSURE® pudding, cottage cheese, yogurt, or strained pears and swallowed immediately. The granules should not be chewed or crushed. Alternatively, PREVACID Delayed-Release Capsules may be emptied into a small volume of either orange juice or tomato juice (60 mL – approximately 2 ounces), mixed briefly and swallowed immediately. To insure complete delivery of the dose, the glass should be rinsed with two or more volumes of juice and the contents swallowed immediately. The granules have also been shown *in vitro* to remain intact when exposed to apple, cranberry, grape, orange, pineapple, prune, tomato, and V-8® vegetable juice and stored for up to 30 minutes.

PREVACID for Delayed-Release Oral Suspension

In addition, for patients who have difficulty swallowing capsules, PREVACID for Delayed-Release Oral Suspension is available in strengths of 15 mg and 30 mg. Directions for use: Empty packet contents into a container containing 2 tablespoons of **WATER**. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well, and drink immediately. DO NOT CRUSH OR CHEW THE GRANULES. If any material remains after drinking, add more water, stir, and drink immediately.

Drug Interactions

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release Capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy: Teratogenic Effects.

Pregnancy Category B

Lansoprazole

Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pregnancy Category C

Clarithromycin

See **WARNINGS** (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Over 4,000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

Use in Geriatric Patients

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

ADVERSE REACTIONS

Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in PREVACID-treated patients than placebo-treated patients:

Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies

Body System/Adverse Event	PREVACID (N= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 mg and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of PREVACID for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID was 5%, misoprostol 22%, and placebo 3%.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to **Postmarketing** for adverse reactions occurring since the drug was marketed.

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain; *Cardiovascular System* – angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/ hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; *Digestive System* – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis; *Endocrine System* – diabetes mellitus, goiter, hypothyroidism; *Hemic and Lymphatic System* – anemia, hemolysis, lymphadenopathy; *Metabolic and Nutritional Disorders* – gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss; *Musculoskeletal System* – arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis; *Nervous System* – abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/ increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo; *Respiratory System* – asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor; *Skin and Appendages* – acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria; *Special Senses* – abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect; *Urogenital System* – abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing

On-going Safety Surveillance: Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole – anaphylactoid-like reaction; *Digestive System* – hepatotoxicity, vomiting; *Hemic and Lymphatic System* – agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Special Senses* – speech disorder; *Urogenital System* – urinary retention.

Combination Therapy with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID, amoxicillin, or clarithromycin.

Triple Therapy: PREVACID/amoxicillin/clarithromycin

The most frequently reported adverse events for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: PREVACID/amoxicillin

The most frequently reported adverse events for patients who received PREVACID t.i.d. plus amoxicillin t.i.d. dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with PREVACID t.i.d. plus amoxicillin t.i.d. dual therapy than with PREVACID alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** sections.

Laboratory Values

The following changes in laboratory parameters for lansoprazole were reported as adverse events:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID plus amoxicillin and clarithromycin, and PREVACID plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory value changes with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** section.

OVERDOSAGE

Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

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Ref. 03-5133-R17-Rev. September, 2001

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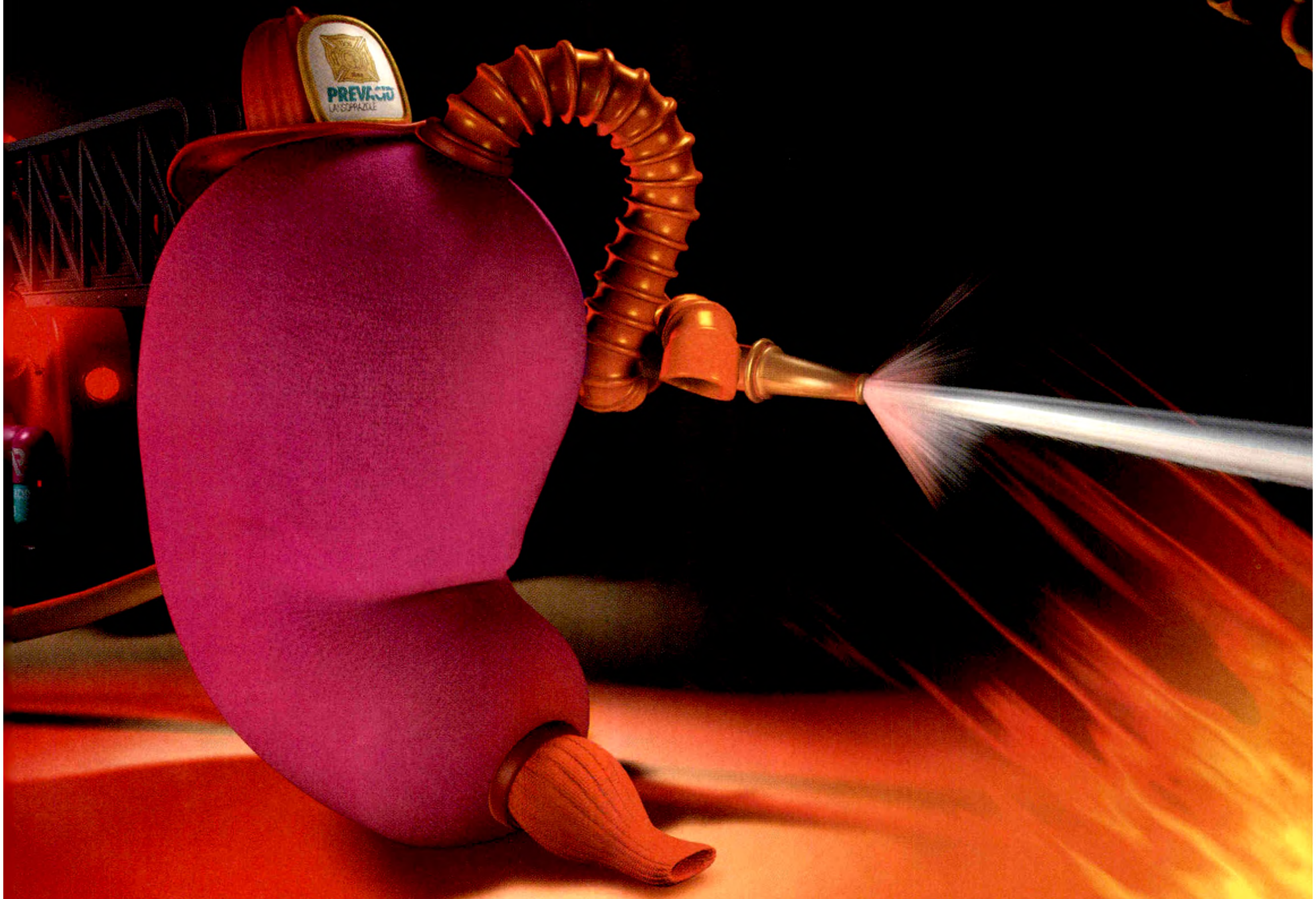

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REFERENCES: 1. PREVACID Complete Prescribing Information. 2. Earnest DL, Dorsch E, Jones J, et al. *Am J Gastroenterol.* 1998;93:238-243. 3. Robinson M, Sahba B, Avner D, et al. *Aliment Pharmacol Ther.* 1995;9:25-31. 4. PRILOSEC® (omeprazole) Complete Prescribing Information. 5. ACIPHEX® (rabeprazole sodium) Complete Prescribing Information. 6. PROTONIX® (pantoprazole sodium) Complete Prescribing Information. 7. NEXIUM™ (esomeprazole magnesium) Complete Prescribing Information. 8. PROTONIX® IV (pantoprazole sodium) Complete Prescribing Information.

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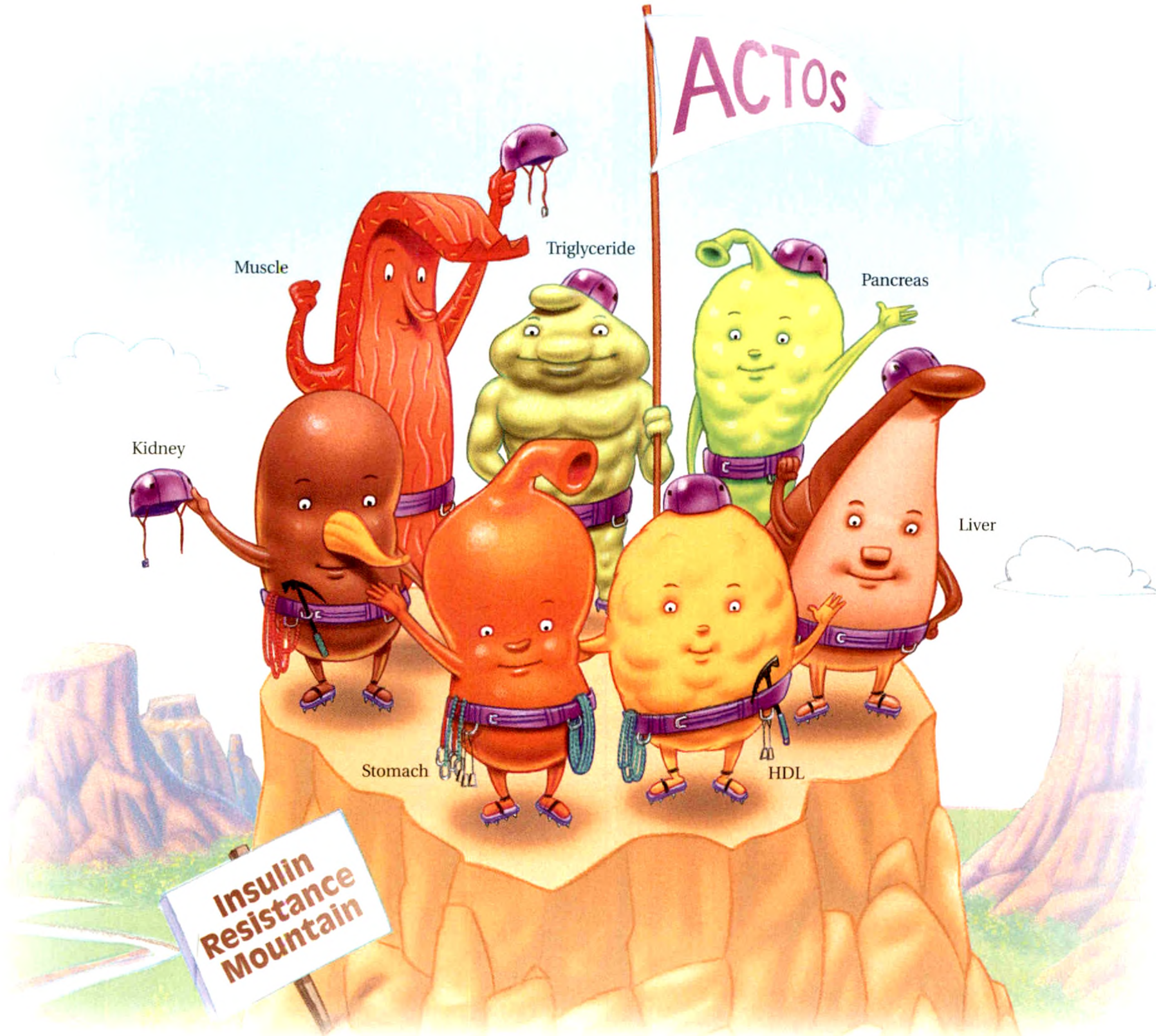
When insulin resistance is an uphill struggle for patients with type 2 diabetes...

Address the challenge with ACTOS



- ACTOS, like other thiazolidinediones (TZDs), can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure, and ACTOS should be discontinued if any deterioration in cardiac status occurs.[1] ● ACTOS is not recommended in patients with NYHA Class III and IV cardiac status.[1] ● A small number of patients with a history of previously existing cardiac disease were reported to develop congestive heart failure when treated with ACTOS in combination with insulin. Reports of congestive heart failure have been received in postmarketing experience in patients with and without previously known heart disease.[1]
- Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received in postmarketing experience. Very rarely, these reports have involved hepatic failure with or without fatal outcome, although causality has not been established.[1] ● Because ACTOS is a member of the TZD class, monitoring of liver enzymes is recommended at baseline, every 2 months for the first year, and periodically thereafter.[1] ● ACTOS should not be initiated in patients exhibiting clinical evidence of active liver disease or if ALT levels >2.5X ULN. Please see PRECAUTIONS section in adjacent brief summary of Prescribing Information.[1]
- The major metabolic defects in type 2 diabetes are peripheral insulin resistance in muscle and fat, decreased pancreatic insulin secretion, and increased hepatic glucose output. Dyslipidemia in insulin resistance is represented by hypertriglyceridemia, decreased HDL levels, and increased small dense LDL particles.[2] Clinical considerations regarding renal and gastrointestinal function are also common concerns when prescribing an oral agent for type 2 diabetes.[3] ● As an adjunct to diet and exercise, ACTOS may be used as monotherapy to lower blood glucose, and in combination with sulfonylureas, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control. ACTOS should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.[1]

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References: 1. ACTOS package insert, Takeda Pharmaceuticals America, Inc. **2.** Haffner SM, D'Agostino R Jr, Mykkänen L, et al. Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 1999;22:562-568. **3.** American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2002;25(suppl 1):S33-S49.

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Brief summary of prescribing information
5012100-04

ACTOS®

(pioglitazone hydrochloride) Tablets

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials; therefore, ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin were compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction.

Analysis of data from this study did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median (25th/75th percentile)	**Median (25th/75th percentile)**	**Median (25th/75th percentile)**	**Median (25th/75th percentile)**
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9 (-0.5/3.4) n=79	1.0 (-0.9/3.4) n=188	2.6 (0.2/5.4) n=79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	2.7 (1.1/4.5) n=186	N/A
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	1.4 (-0.9/3.0) n=167	N/A
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.6 (1.4/5.9) n=188	N/A

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, has been associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death have been reported during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and very rare cases of reversible jaundice were reported.

In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 2500 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants and death during postmarketing clinical use.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients, every two months for the first year of therapy, and periodically thereafter. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests

FBG and HbA$_{1c}$ measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy, every two months for the first year, and periodically thereafter. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions

Oral Contraceptives. Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of coadministration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

Glipizide: In healthy volunteers, coadministration of ACTOS (45 mg once daily) and glipizide (5.0 mg once daily) for seven days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: In healthy volunteers, coadministration of ACTOS (45 mg once daily) with digoxin (0.25 mg once daily) for seven days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: In healthy volunteers, coadministration of ACTOS (45 mg once daily) for seven days with warfarin did not alter the steady-state pharmacokinetics of warfarin. In addition, ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: In healthy volunteers, coadministration of metformin (1000 mg) and ACTOS (45 mg) after seven days of ACTOS (45 mg once daily) did not alter the pharmacokinetics of the single dose of metformin.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism). Pending the availability of additional data, patients receiving ketoconazole concomitantly with ACTOS should be evaluated more frequently with respect to glycemic control.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). The relationship of these findings in male rats to humans is unclear. A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use

Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In worldwide clinical trials, over 3700 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 2500 patients have received ACTOS, over 1100 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated With ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In the ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

Mild to moderate hypoglycemia was reported during combination therapy with sulfonylurea or insulin. Hypoglycemia was reported for 1% of placebo-treated patients and 2% of patients when ACTOS was used in combination with a sulfonylurea. In combination with insulin, hypoglycemia was reported for 5% of placebo-treated patients, 8% for patients treated with 15 mg of ACTOS, and 15% for patients treated with 30 mg of ACTOS (see PRECAUTIONS, General, Hypoglycemia).

In U.S. double-blind studies, anemia was reported for 1.0% of patients treated with ACTOS and 0.0% of placebo-treated patients in monotherapy studies. Anemia was reported for 1.6% of patients treated with ACTOS and 1.6% of placebo-treated patients in combination with insulin. Anemia was reported for 0.3% of patients treated with ACTOS and 1.6% of placebo-treated patients in combination with sulfonylurea. Anemia was reported for 1.2% of patients treated with ACTOS and 0.0% of placebo-treated patients in combination with metformin.

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have not been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. During all clinical studies in the U.S., 11 of 2561 (0.43%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.12% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. A single, isolated elevation to greater than 10 times the upper limit of normal (values of 2150 to 8610) was noted in 7 patients. Five of these patients continued to receive ACTOS and the other two patients had completed receiving study medication at the time of the elevated value. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

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1. Conceived and planned the work that led to the article or played an important role in interpreting the results, or both.
2. Wrote the paper and/or made substantive suggestions for revision.
3. Approved the final version.

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For Authors and Their Institutions

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Annals of Internal Medicine | Summaries for Patients

Treatment of Fever in Hospitalized Patients with Low White Blood Cell Counts

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Ciprofloxacin plus Piperacillin Compared with Tobramycin plus Piperacillin as Empirical Therapy in Febrile Neutropenic Patients. A Randomized, Double-Blind Trial." It is in the 16 July 2002 issue of *Annals of Internal Medicine* (volume 137, pages 77-86). The authors are JE Peacock Jr, DA Herrington, JC Wade, HM Lazarus, MD Reed, JW Sinclair, DC Haverstock, SF Kowalsky, DD Hurd, DA Cushing, CP Harman, and GR Donowitz.

What is the problem and what is known about it so far?

Types of cancer, such as leukemia, and the therapies used to treat them (for example, chemotherapy and bone marrow transplants) often decrease the numbers of white blood cells in the body. White blood cells fight bacterial, fungal, and viral infections. Most patients with cancer who have few white blood cells have very weak immune systems and can't fight infections well. They get infections easily and, as a result, can die, particularly if the infections are not recognized early and treated. Fever is usually one of the earliest signs of infection. Thus, doctors prescribe powerful antibiotics whenever they detect a fever and suspect an infection in a patient with cancer whose white blood cell count is low. Doctors usually give combinations of antibiotics that work against many different types of bacteria. We do not know whether certain combinations work better and cause fewer side effects than others.

Why did the researchers do this particular study?

To compare two different combinations of antibiotic drugs for treating fever in hospitalized patients with low white blood cell counts.

Who was studied?

485 hospitalized patients with cancer and a low number of white blood cells. Most had leukemia or had received bone marrow transplants. All had fever that was presumed to have been caused by infection.

How was the study done?

Patients were randomly assigned to receive one of two combinations of antibiotic drugs (piperacillin plus ciprofloxacin or piperacillin plus tobramycin). The drugs were given through a vein. The patients and their doctors did not know which drug combination the patients were receiving. The researchers compared treatment responses and adverse side effects between patients who were given the two different drug combinations. The researchers considered the patients' treatment response to be successful if they had no fever for at least 4 days, resolution of signs of infection without having to change the initial antibiotic drugs, and a negative culture from the blood or the original infection site.

What did the researchers find?

Nearly 25% of the patients in both groups had successful treatment responses. Fever resolved more quickly (approximately 1 day sooner) in patients given pipericillin plus ciprofloxacin. Four percent of the patients in each group died. Approximately 70% in each group needed additional therapy with other antibiotic or antifungal drugs. Medication-related side effects, such as diarrhea and abnormal results on kidney and liver function tests, occurred in approximately 20% to 30% of patients in both groups.

What were the limitations of the study?

Many patients in both groups needed therapy other than their originally assigned antibiotic combinations. In such instances, it is difficult to sort out how effective the original antibiotic combinations were.

What are the implications of the study?

Piperacillin plus ciprofloxacin and piperacillin plus tobramycin have similar efficacy and safety for hospitalized patients with low white blood cell counts and fever.

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SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.

Safety Information

Co-administration with astemizole, cisapride, midozolam, triazolam or ergot derivatives is contraindicated. 53% of patients reported nervous system symptoms when taking SUSTIVA. Generally mild to moderate, they usually begin during Days 1-2 and resolve after 2 to 4 weeks. Serious psychiatric experiences occur in a small number of patients (≤1.6% for specific events). There have been a few reports of suicide, but SUSTIVA has not been established as a cause. Nervous system symptoms are not predictive of these less frequent psychiatric symptoms. Mild to moderate rash is another common side effect of SUSTIVA. Women should not become pregnant or breast-feed while taking SUSTIVA. The use of SUSTIVA and St. John's wort (*hypericum perforatum*)-containing products is not recommended.

Please see brief summary of full prescribing information for SUSTIVA on adjacent page.

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INDICATIONS AND USAGE

SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV-RNA.

CONTRAINDICATIONS

SUSTIVA is contraindicated in patients with clinically significant hypersensitivity to any of its components.

SUSTIVA should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (e.g., cardiac arrhythmias, prolonged sedation or respiratory depression).

WARNINGS

ALERT: Find out about medicines that should NOT be taken with SUSTIVA. This statement is also included on the product's bottle labels. (See **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**.)

SUSTIVA must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials of 1008 patients treated with regimens containing SUSTIVA for an average of 1.6 years and 635 patients treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events among patients who received SUSTIVA or control regimens, respectively, were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), nonfatal suicide attempts (0.4%, 0%), aggressive behavior (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%) and manic reactions (0.1%, 0%). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been occasional post-marketing reports of death by suicide, delusions and psychosis-like behavior, although a causal relationship to the use of SUSTIVA cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **ADVERSE REACTIONS**).

Nervous System Symptoms: Fifty-three percent of patients receiving SUSTIVA in controlled trials reported central nervous system symptoms compared to 25% of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%) and hallucinations (1.2%). These symptoms were severe in 2.0% of patients and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5-9% in patients treated with regimens containing SUSTIVA and from 3-5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** in full prescribing information).

Patients receiving SUSTIVA should be alerted to the potential for additive central nervous system effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

Drug Interactions: Concomitant use of SUSTIVA and St. John's wort (*hypericum perforatum*) or St. John's wort-containing products is not recommended. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including SUSTIVA, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Reproductive Risk Potential: Malformations have been observed in fetuses from efavirenz-treated monkeys that received doses which resulted in plasma drug concentrations similar to those in humans given 600 mg/day (see **PRECAUTIONS: Pregnancy**); therefore, pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of SUSTIVA.

PRECAUTIONS

General:

Skin Rash- In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg SUSTIVA experienced new onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson Syndrome) in patients treated with SUSTIVA in all studies and expanded access was 0.1%. The median time to onset of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with SUSTIVA capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was eight days. Prophylaxis with appropriate antihistamines prior to initiating therapy with SUSTIVA in pediatric patients should be considered (see **ADVERSE REACTIONS**).

Liver Enzymes- In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with SUSTIVA needs to be weighed against the unknown risks of significant liver toxicity (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering SUSTIVA (efavirenz) to these patients.

Cholesterol- Monitoring of cholesterol and triglycerides should be considered in patients treated with SUSTIVA (see **ADVERSE REACTIONS**).

Fat Redistribution- Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients: A statement to patients and healthcare providers is included on the product's bottle labels: **ALERT: Find out about medicines that should NOT be taken with SUSTIVA.** A Patient Package Insert (PPI) for SUSTIVA is available for patient information.

Patients should be informed that SUSTIVA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that there are currently no data demonstrating that SUSTIVA therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take SUSTIVA every day as prescribed. SUSTIVA must always be used in combination with other antiretroviral drugs. Patients should be advised to take SUSTIVA on an empty stomach, preferably at bedtime. Taking SUSTIVA with food increases efavirenz concentrations and may increase the frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** in full prescribing information). Patients should remain under the care of a physician while taking SUSTIVA.

Patients should be informed that central nervous system symptoms including dizziness, insomnia, impaired concentration, drowsiness and abnormal dreams are commonly reported during the first weeks of therapy with SUSTIVA. Dosing at bedtime may improve the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery (see **WARNINGS: Nervous System Symptoms**). In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**).

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia and psychosis-like symptoms have also been infrequently reported in patients receiving SUSTIVA. Patients should be informed that if they experience severe psychiatric adverse experiences they should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine whether discontinuation of SUSTIVA may be required. Patients should also inform their physician of any history of mental illness or substance abuse (see **WARNINGS: Psychiatric Symptoms**).

Patients should be informed that another common side effect is rash. These rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. Patients should be advised that they should contact their physician promptly if they develop a rash.

Because malformations have been observed in fetuses from efavirenz-treated animals, instructions should be given to avoid pregnancy in women receiving SUSTIVA. Women should be advised to notify their physician if they become pregnant while taking SUSTIVA. A reliable form of barrier contraception should always be used in combination with other methods of contraception, including oral or other hormonal contraception because the effects of efavirenz on hormonal contraceptives are not fully characterized.

SUSTIVA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication or herbal products, particularly St. John's wort.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions (see also **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interactions** in full prescribing information): Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with SUSTIVA. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with SUSTIVA are summarized in Table 1.

Table 1*
Drugs That Should Not Be Coadministered With SUSTIVA

Drug Class	Drugs Within Class Not To Be Coadministered With SUSTIVA
Antihistamines	astemizole
Benzodiazepines	midazolam, triazolam
GI Motility Agents	cisapride
Anti-Migraine	ergot derivatives

Established Drug Interactions

Drug Name	Effect	Clinical Comment
Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Plasma concentrations decreased by SUSTIVA; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving SUSTIVA and clarithromycin. No dose adjustment of SUSTIVA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see **Other Drugs**, following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with SUSTIVA.
Indinavir	↓ indinavir concentration	Increase indinavir dose from 800 mg to 1000 mg every 8 hours.
Methadone	↓ methadone concentration	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Ethinyl estradiol	↑ ethinyl estradiol concentration	Plasma concentrations increased by SUSTIVA; clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentrations unknown.
Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	Combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when SUSTIVA is used in combination with ritonavir.
Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with SUSTIVA.
Other Potentially Clinically Significant Drug or Herbal Product Interactions With SUSTIVA**		
Anticoagulants: Warfarin		Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants: Phenytoin Phenobarbital Carbamazepine		Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antifungals: Itraconazole Ketoconazole		Drug interaction studies with SUSTIVA and these imidazole and triazole antifungals have not been conducted. SUSTIVA has the potential to decrease plasma concentrations of itraconazole and ketoconazole.
Anti-HIV protease inhibitors: Saquinavir/ritonavir combination		No pharmacokinetic data are available.
Amprenavir		SUSTIVA has the potential to decrease serum concentrations of amprenavir.
Non-nucleoside reverse transcriptase inhibitors		No studies have been performed with other NNRTIs.
St. John's wort *(hypericum perforatum)*		Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with SUSTIVA.

* See Tables 1 and 2 in full prescribing information.

** This table is not all-inclusive.

Other Drugs- Based on the results of drug interaction studies (see Tables 1 and 2 in full prescribing information), no dosage adjustment is recommended when SUSTIVA is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, and zidovudine.

Specific drug interaction studies have not been performed with SUSTIVA and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

Efavirenz was not mutagenic or genotoxic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese Hamster Ovary cells, chromosomal aberration assays in human peripheral blood lymphocytes or Chinese Hamster Ovary cells, and an *in vivo* mouse bone marrow micronucleus assay.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Pregnancy:

Pregnancy "Category C"- Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (post coital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of SUSTIVA (efavirenz). Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those seen in the clinic at the recommended dose, pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of SUSTIVA (see **WARNINGS: Reproductive Risk Potential**).

Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to, or lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to, and AUC values approximately half of those achieved in humans given 600 mg once daily of SUSTIVA.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to SUSTIVA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, **mothers should be instructed not to breast-feed if they are receiving SUSTIVA.**

Pediatric Use: ACTG 382 is an ongoing open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range 3-16). SUSTIVA has not been studied in pediatric patients below 3 years of age or who weigh less than 13 Kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults (see **ADVERSE REACTIONS: Table 3**).

The starting dose of SUSTIVA was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 µM•h. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600 mg daily doses of SUSTIVA. In 48 pediatric patients receiving the equivalent of a 600 mg dose of SUSTIVA, steady-state C_{max} was 14.2 ± 5.8 µM (mean ± S.D.), steady-state C_{min} was 5.6 ± 4.1 µM, and AUC was 218 ± 104 µM•h.

Geriatric Use: Clinical studies of SUSTIVA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

ADVERSE REACTIONS

The most significant adverse events observed in patients treated with SUSTIVA are nervous system symptoms, psychiatric symptoms, and rash.

Nervous System Symptoms: Fifty-three percent of patients receiving SUSTIVA reported central nervous system symptoms (see **WARNINGS: Nervous System Symptoms**). Table 2 lists the frequency of the symptoms of different degrees of severity, and gives the discontinuation rates, in clinical trials for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 4.

Table 2
Percent of Patients with One or More Selected Nervous System Symptoms[1,2]

Percent of Patients with:	SUSTIVA 600 mg Once Daily (N=1008) %	Control Groups (N=635) %
Symptoms of Any Severity	52.7	24.6
Mild Symptoms[3]	33.3	15.6
Moderate Symptoms[4]	17.4	7.7
Severe Symptoms[5]	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[1] Includes events reported regardless of causality.
[2] Data from Study 006 and three Phase 2/3 studies.
[3] "Mild" = Symptoms which do not interfere with patient's daily activities.
[4] "Moderate" = Symptoms which may interfere with daily activities.
[5] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials the frequency of specific serious psychiatric symptoms among patients who received SUSTIVA or control regimens, respectively, were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), non-fatal suicide attempts (0.4%, 0%), aggressive behavior (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%) and manic reactions (0.1%, 0%) (see **WARNINGS: Psychiatric Symptoms**). Additional psychiatric symptoms observed at a frequency of >2% among patients treated with SUSTIVA (efavirenz) or control regimens, respectively, in controlled clinical trials were depression (15.8%, 13.1%), anxiety (11.1%, 7.6%), and nervousness (6.3%, 2.0%).

Skin Rash: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with SUSTIVA. In most patients, rash resolves with continuing SUSTIVA therapy within one month. SUSTIVA can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids may be considered when SUSTIVA is restarted. SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in Table 3.

Table 3
Percent of Patients with Treatment-Emergent Rash[1,2]

Percent of Patients with:	Description of Rash Grade[3]	SUSTIVA 600 mg Once Daily Adults (N=1008) %	SUSTIVA Pediatric Patients (N=57) %	Control Groups Adults (N=635) %
Rash of Any Grade	–	26.3	45.6	17.5
Grade 1 Rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 Rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 Rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3
Grade 4 Rash	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0.0
Treatment discontinuation as a result of rash	–	1.7	8.8	0.3

[1] Includes events reported regardless of causality.
[2] Data from Study 006 and three Phase 2/3 studies.
[3] NCI Grading System.

As seen in Table 3, rash is more common in pediatric patients and more often of higher grade (i.e., more severe) (see **PRECAUTIONS: General**).

Experience with SUSTIVA in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with SUSTIVA. Nine of these patients developed mild-to-moderate rash while receiving therapy with SUSTIVA, and two of these patients discontinued because of rash.

A few cases of pancreatitis have been described, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

Drug-related clinical adverse experiences of moderate or severe intensity observed in ≥2% of patients in two controlled clinical trials are presented in Table 4.

Table 4
Percent of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Patients in Studies 006 and ACTG 364

Adverse Events	Study 006 LAM, NNRTI and Protease Inhibitor Naive Patients			Study ACTG 364 NRTI-experienced NNRTI and Protease Inhibitor Naive Patients		
	SUSTIVA[2] + ZDV/LAM (N=412) %	SUSTIVA[2] + Indinavir (N=415) %	Indinavir + ZDV/LAM (N=401) %	SUSTIVA[2] + Nelfinavir + NRTIs (N=64) %	SUSTIVA[2] + NRTIs (N=65) %	Nelfinavir + NRTIs (N=66) %
Body as a Whole						
Fatigue	7	5	8	0	2	3
Pain	1	1	5	13	6	17
Central and Peripheral Nervous System						
Dizziness	8	8	3	2	6	6
Headache	7	4	4	5	2	3
Concentration Impaired	5	2	0	0	0	0
Insomnia	6	7	3	0	0	2
Abnormal Dreams	3	1	0	–	–	–
Somnolence	3	2	2	0	0	0
Anorexia	1	0	1	0	2	2
Gastrointestinal						
Nausea	12	7	25	3	2	2
Vomiting	7	6	14	–	–	–
Diarrhea	6	8	6	14	3	9
Dyspepsia	3	3	5	0	0	2
Abdominal Pain	1	2	4	3	3	3
Psychiatric						
Anxiety	1	3	0	–	–	–
Depression	2	1	0	3	0	5
Nervousness	2	2	0	2	0	2
Skin & Appendages						
Rash	13	20	7	9	5	9
Pruritus	0	1	1	9	5	9
Increased Sweating	2	1	0	0	0	0

[1] Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.
[2] SUSTIVA provided as 600 mg Once Daily.
– = Not Specified.

In Study 006, lipodystrophy was reported in 2.3% of patients treated with SUSTIVA (efavirenz)+IDV, 0.7% of patients treated with SUSTIVA+ZDV+LAM and 1.0% of patients treated with IDV+ZDV+LAM.

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received SUSTIVA capsules, nelfinavir, and one or more NRTIs were: rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash (see also **PRECAUTIONS: Skin Rash** and **Pediatric Use**).

Post-Marketing Experience:

Body as a Whole- allergic reactions, asthenia, redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Central and Peripheral Nervous System- abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, tremor

Endocrine- gynecomastia

Gastrointestinal- constipation, malabsorption

Cardiovascular- flushing, palpitations

Liver and Biliary System- hepatic enzyme increase, hepatic failure, hepatitis

Metabolic and Nutritional- hypercholesterolemia, hypertriglyceridemia

Musculoskeletal- arthralgia, myalgia, myopathy

Psychiatric- aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory- dyspnea

Skin and Appendages- erythema multiforme, nail disorders, skin discoloration, Stevens-Johnson Syndrome

Special Senses- abnormal vision, tinnitus

Laboratory Abnormalities:

Liver Enzymes- Among 1008 patients treated with 600 mg efavirenz in controlled clinical trials, 3% developed AST levels and 3% developed ALT levels greater than five times the upper limit of normal. Similar elevations of AST and ALT were seen in patients treated with control regimens.

Liver function tests should be monitored in patients with a prior history of Hepatitis B and/or C. In 156 patients treated with 600 mg of SUSTIVA who were seropositive for Hepatitis B and/or C, 7% developed AST levels and 8% developed ALT levels greater than five times the upper limit of normal. In 91 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 4% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of SUSTIVA and in 10% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 1.5-2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving SUSTIVA may reflect enzyme induction not associated with liver toxicity (see **PRECAUTIONS: General**).

Lipids- Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving SUSTIVA. In patients treated with SUSTIVA+ZDV+LAM, increases in non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with SUSTIVA+IDV, increases in non-fasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. The effects of SUSTIVA on triglycerides and LDL were not well-characterized since samples were taken from non-fasting patients. The clinical significance of these findings is unknown (see **PRECAUTIONS: General**).

Serum Amylase- Asymptomatic elevations in serum amylase greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with SUSTIVA and in 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown (see **ADVERSE REACTIONS**).

Cannabinoid Test Interaction- Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received SUSTIVA. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

OVERDOSAGE

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with SUSTIVA should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with SUSTIVA. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

HOW SUPPLIED

Capsules: SUSTIVA® (efavirenz) capsules are available as follows:

Capsules 200 mg are gold color, reverse printed with "SUSTIVA" on the body and imprinted "200 mg" on the cap.

Bottles of 90	**NDC** 0056-0474-92

Capsules 100 mg are white, reverse printed with "SUSTIVA" on the body and imprinted "100 mg" on the cap.

Bottles of 30	**NDC** 0056-0473-30

Capsules 50 mg are gold color and white, printed with "SUSTIVA" on the gold color cap and reverse printed "50 mg" on the white body.

Bottles of 30	**NDC** 0056-0470-30

Tablets: SUSTIVA® (efavirenz) tablets are available as follows:

Tablets 600 mg are yellow, capsular-shaped, film-coated tablets, with "SUSTIVA" printed on both sides.

Bottles of 30	**NDC** 0056-0510-30
Unit-Dose blister package of 100	**NDC** 0056-0510-76

SUSTIVA capsules and SUSTIVA tablets should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Distributed by:

BMS Virology™
Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

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Annals of Internal Medicine

SUMMARIES FOR PATIENTS

A Decision Aid for Recognizing and Treating Heart Attacks Quickly

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Use of the Electrocardiograph-Based Thrombolytic Predictive Instrument To Assist Thrombolytic and Reperfusion Therapy for Acute Myocardial Infarction. A Multicenter, Randomized, Controlled, Clinical Effectiveness Trial." It is in the 16 July 2002 issue of *Annals of Internal Medicine* (volume 137, pages 87-95). The authors are HP Selker, JR Beshansky, and JL Griffith, for the TPI Trial Investigators.

What is the problem and what is known about it so far?

Heart attacks occur when blood flow through the arteries to the heart (coronary arteries) is blocked long enough to damage a portion of heart muscle. Heart attacks usually cause symptoms such as severe chest pain, nausea, shortness of breath, or a feeling of impending doom. Most people with heart attacks also have abnormal heart tracings (electrocardiograms [ECGs]) that suggest poor blood flow to the heart.

Recognizing heart attacks quickly is important. If given within a few hours of a heart attack, special "clot-buster" drugs (thrombolytics) and procedures with balloon catheters (angioplasty) can open up coronary arteries, reduce heart muscle damage, and save lives. Special decision aids may help doctors diagnose and treat heart attacks quickly. Some of the aids use formulas to estimate the chances of particular treatment outcomes based on each patient's age, sex, history, blood pressure, and ECG. Although they seem like a good idea, we do not know whether routine use of these aids changes the care that patients actually receive.

Why did the researchers do this particular study?

To see whether a decision aid (the Thrombolytic Predictive Instrument) that helps doctors predict outcomes of thrombolytic therapy actually increases the use of clot-buster drugs, angioplasty, or both.

Who was studied?

1197 adults from 28 urban, suburban, and rural emergency rooms who had ECGs that suggested an acute heart attack.

How was the study done?

Patients were randomly assigned to receive either usual care or care guided by the decision aid. Doctors obtained ECGs for all patients. For those assigned to the decision aid, researchers entered the following information into a computerized ECG machine: age, sex, history of high blood pressure and diabetes, and when heart attack symptoms began. The computer printout of the ECG for these patients showed doctors the chances of death, stroke, and bleeding with and without thrombolytic therapy. The researchers then followed patients in both groups to see which ones got thrombolytic therapy, angioplasty, or both.

What did the researchers find?

About 60% of the patients in both groups got thrombolytic therapy. An additional 7% to 8% in both groups had angioplasty. The decision aid compared with usual care increased use of thrombolytic therapy in certain subgroups of patients, including women, those whose heart attack was on the bottom (inferior) part of the heart, and those who were seen in hospitals that did not have expert heart doctors available on site.

What were the limitations of the study?

The decision aid predicted outcomes of only one type of treatment (thrombolytic therapy). Many doctors use other treatments for acute heart attacks. The study was not large enough to test whether using the decision aid reduced deaths from heart attacks.

What are the implications of the study?

Providing patient-specific predictions of thrombolytic outcomes to doctors increases use of thrombolytic therapy only in certain types of patients.

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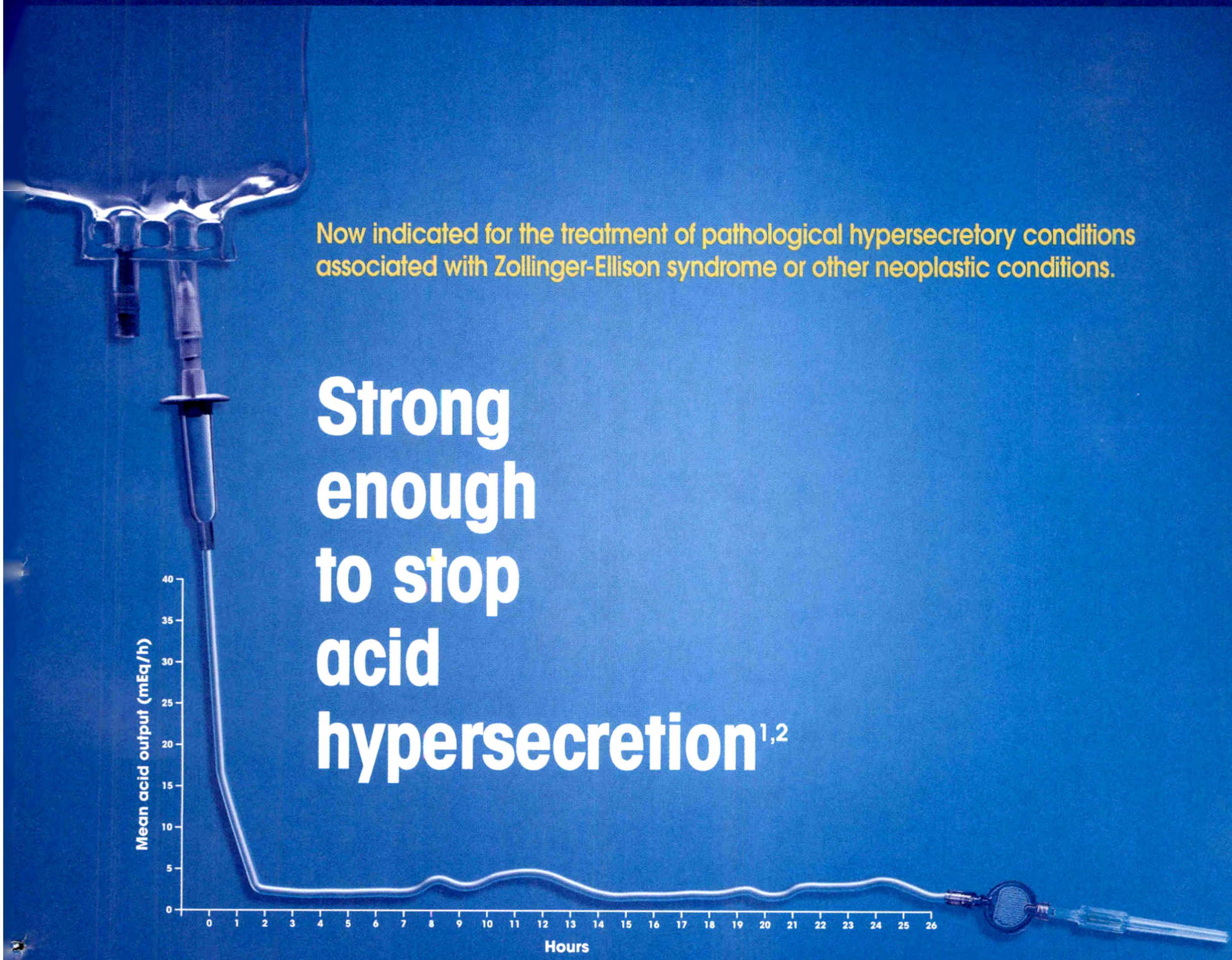
New Indication

Now indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions.

Strong enough to stop acid hypersecretion[1,2]



n = 17/21 PROTONIX I.V. 80 mg q12h (Four patients required 240 mg/day)

PROTONIX I.V.
(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

In clinical trials, the most frequently reported adverse events with PROTONIX I.V. were injection site reactions (including thrombophlebitis and abscess), headache, diarrhea, nausea, and dyspepsia. PROTONIX I.V. is contraindicated in patients with known hypersensitivity to any component of the formulation. Anaphylaxis has been reported. Treatment with PROTONIX I.V. should be discontinued as soon as the patient is able to be treated with PROTONIX Delayed-Release Tablets. **Please see brief summary of Prescribing Information on adjacent page.**

PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

See package insert for full prescribing information

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

Short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis, **as an alternative to oral therapy in patients who are unable to continue taking PROTONIX (pantoprazole sodium) Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment of patients having GERD with a history of erosive esophagitis have not been demonstrated.

Pathological Hypersecretion Associated With Zollinger-Ellison Syndrome

Treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions.

CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Immediate hypersensitivity reactions: Anaphylaxis has been reported with use of intravenous pantoprazole. This may require emergency medical treatment.

Injection site reactions: Thrombophlebitis was associated with the administration of intravenous pantoprazole.

Hepatic effects: Mild, transient transaminase elevations have been observed in clinical studies. The clinical significance of this finding in a large population of subjects administered intravenous pantoprazole is unknown. (See **ADVERSE REACTIONS** section.)

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets.

Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month oral toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay. A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

No gender-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 166 men and 120 women with GERD. Erosive esophagitis healing rates in the 221 women treated with oral pantoprazole in U.S. clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly

No age-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 86 elderly (≥ 65 years old) and 200 younger (< 65 years old) patients with erosive esophagitis associated with GERD. Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with oral pantoprazole in U.S. clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

ADVERSE REACTIONS

Safety Experience With Intravenous Pantoprazole

Intravenous pantoprazole has been studied in clinical trials in several populations including patients having GERD with a history of erosive esophagitis, patients with Zollinger-Ellison syndrome, and healthy subjects. Adverse experiences occurring in >1% of patients treated with intravenous pantoprazole (n=714) in domestic and international clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abdominal pain, headache, injection site reaction (including thrombophlebitis and abscess)

DIGESTIVE SYSTEM: constipation, dyspepsia, nausea, diarrhea.

NERVOUS SYSTEM: insomnia.

RESPIRATORY SYSTEM: rhinitis

Head-to-head comparative studies between PROTONIX I.V. for Injection and oral PROTONIX, other proton pump inhibitors (oral or I.V.), or H2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

Safety Experience With Oral Pantoprazole

In short-term clinical trials in patients with erosive esophagitis associated with GERD treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of ≥1%.

BODY AS A WHOLE: headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain

CARDIOVASCULAR SYSTEM: migraine.

DIGESTIVE SYSTEM: diarrhea, flatulence, abdominal pain, eructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

HEPATO-BILIARY SYSTEM: liver function tests abnormal, SGPT increased

METABOLIC AND NUTRITIONAL: hyperglycemia, hyperlipidemia.

MUSCULOSKELETAL SYSTEM: arthralgia.

NERVOUS SYSTEM: insomnia, anxiety, dizziness, hypertonia

RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection

SKIN AND APPENDAGES: rash

UROGENITAL SYSTEM: urinary frequency, and urinary tract infection

Additional adverse experiences occurring in <1% of patients with erosive esophagitis associated with GERD receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis

Postmarketing Reports

The postmarketing safety profile of intravenous pantoprazole (from an estimate of over 700,000 patients) is not substantially different from that of oral pantoprazole (described below).

There have been spontaneous reports of adverse events with postmarketing use of intravenous or oral pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis, pancytopenia, and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In U.S. clinical trials of patients having GERD with a history of erosive esophagitis and international clinical trials of patients with erosive esophagitis associated with GERD, the overall percentages of transaminase elevations did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two U.S. controlled trials of oral pantoprazole in patients with erosive esophagitis associated with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts of pantoprazole (400 and 600 mg) with no adverse effects.

Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

PROTONIX I.V. for Injection admixtures should be administered intravenously through a dedicated line, using the in-line filter provided. **The filter must be used** to remove the precipitate that may form when the reconstituted drug product is mixed with I.V. solutions. Studies have shown that filtration does not alter the amount of drug that is available for administration. If administration through a Y-site is desirable, the in-line filter must be positioned below the Y-site that is closest to the patient. The intravenous line should be flushed before and after administration of PROTONIX I.V. for Injection with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP. PROTONIX I.V. for Injection should not be simultaneously administered through the same line with other intravenous solutions.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets. Also, data on safe and effective dosing for conditions other than those described in **INDICATIONS AND USAGE,** such as life-threatening upper gastrointestinal bleeds, are not available. PROTONIX I.V. 40 mg once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

Parenteral routes of administration other than intravenous are not recommended.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

The recommended adult dose, **as an alternative to continued oral therapy**, is 40-mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. Safety and efficacy of PROTONIX I.V. for Injection as a treatment of patients having GERD with a history of erosive esophagitis for more than 10 days have not been demonstrated (see **INDICATIONS AND USAGE**).

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted (admixed) with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution needs to be protected from light.

PROTONIX I.V. for Injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 3 mg/min (7 mL/min).

Pathological Hypersecretion Associated With Zollinger-Ellison Syndrome

The dosage of PROTONIX I.V. for Injection in patients with pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions varies with individual patients. The recommended adult dosage is 80 mg q12h. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg q8h is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. (See **Clinical Studies** section of full Prescribing Information.) Transition from oral to I.V. and from I.V. to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with Zollinger-Ellison syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

Each vial of PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be combined and further diluted (admixed) with 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution needs to be protected from light.

PROTONIX I.V. for Injection should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 6 mg/min (7 mL/min).

℞ only

US Patent No. 4,758,579

Wyeth®

under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on CI 6005-4 12/20/01

References: **1.** Data on file, Wyeth Pharmaceuticals. **2.** Lew EA, Pisegna JR, Starr JA, et al. Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Gastroenterology*. 2000;118:696-704.

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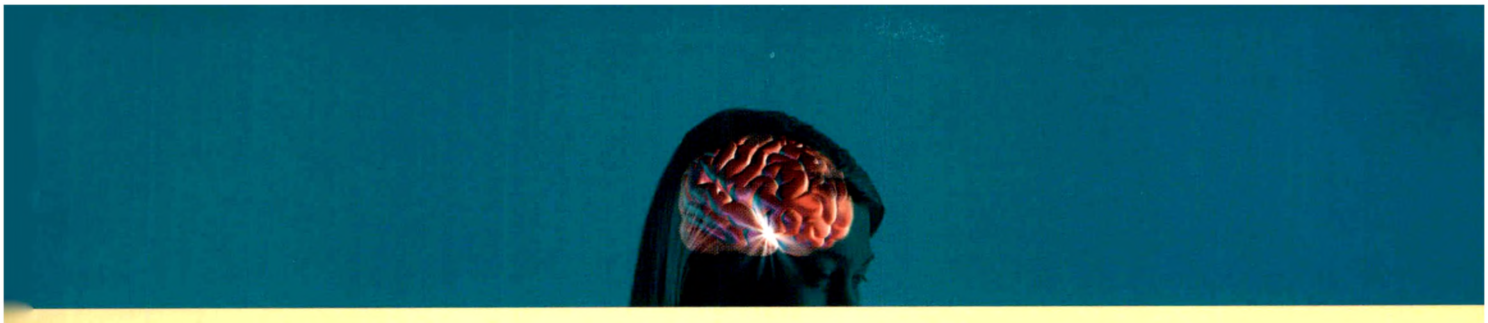
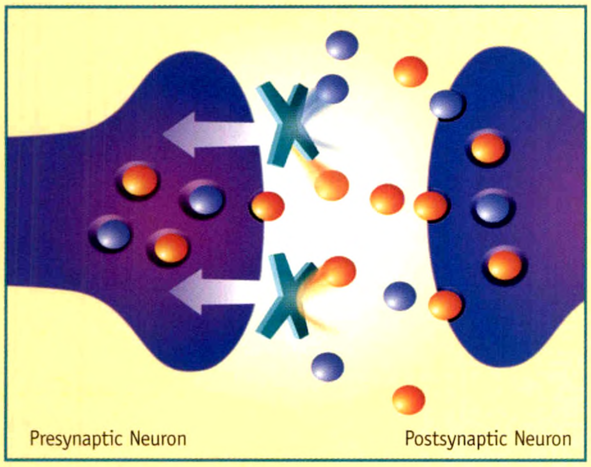


MERIDIA: THE FIRST REUPTAKE INHIBITOR DEVELOPED FOR THE TREATMENT OF OBESITY[1]



- MERIDIA reduces food intake by reuptake inhibition of primarily norepinephrine and serotonin—with no release of monoamines[1]
- MERIDIA works on select receptor sites to help reduce hunger[1]
- 8.5 million patients worldwide have taken sibutramine[2]
- FDA approved since 1997[2]

INDICATIONS AND SAFETY INFORMATION[3]

MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet; it is recommended for obese patients with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs), patients with anorexia nervosa, those with hypersensitivity to sibutramine or its ingredients, and those taking other centrally acting appetite-suppressant drugs.

MERIDIA substantially increases blood pressure in some patients. Regular monitoring of blood pressure is required when prescribing MERIDIA.

MERIDIA should not be used in patients with a history of coronary artery disease, arrhythmias, congestive heart failure, or stroke. MERIDIA should not be used in patients with uncontrolled or poorly controlled hypertension, severe hepatic dysfunction, or severe renal impairment. MERIDIA should be used with caution in patients with narrow-angle glaucoma or a history of seizures.

MERIDIA inhibits serotonin reuptake; in general, it should not be administered with other serotonergic agents. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

Most common adverse events include headache (30%), dry mouth (17%), anorexia (13%), constipation (12%), and insomnia (11%).

References: 1. Heal DJ, Aspley S, Prow MR, et al. Sibutramine: a novel anti-obesity drug. A review of the pharmacological evidence to differentiate it from d-amphetamine and d-fenfluramine. *Int J Obes.* 1998;22(suppl 1):S18-S28. **2.** Data on file, Abbott Laboratories. **3.** MERIDIA Package Insert, Abbott Laboratories.

PLEASE SEE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON THE FOLLOWING PAGE.

MERIDIA® CIV
(sibutramine HCl monohydrate) Capsules

Abbott Laboratories
Abbott Park, IL 60064

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02D-600-3381-1 • April 2002 • Printed in U.S.A.

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

MERIDIA® CIV

(sibutramine hydrochloride monohydrate) Capsules

CONTRAINDICATIONS: MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see "**WARNINGS**").

MERIDIA is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.

MERIDIA is contraindicated in patients who have anorexia nervosa.

MERIDIA is contraindicated in patients taking other centrally acting appetite suppressant drugs.

WARNINGS: Blood Pressure and Pulse: MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE IS REQUIRED WHEN PRESCRIBING MERIDIA.

In placebo-controlled obesity studies, MERIDIA 5 to 20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1 to 3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4 to 5 beats per minute. Larger increases were seen in some patients, particularly when therapy with MERIDIA was initiated at the higher doses (see table below). In pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with MERIDIA were discontinued for hypertension (SBP ≥160 mm Hg or DBP ≥95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with MERIDIA were discontinued for tachycardia (pulse rate ≥100 bpm), compared with 0.1% in the placebo group. Blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension, and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

	% Outliers*		
Dose (mg)	SBP	DBP	Pulse
Placebo	9	7	12
5	6	20	16
10	12	15	28
15	13	17	24
20	14	22	37

* Outlier defined as increase from baseline of ≥15 mm Hg for three consecutive visits (SBP), ≥10 mm Hg for three consecutive visits (DBP), or pulse ≥10 bpm for three consecutive visits.

Potential Interaction With Monoamine Oxidase Inhibitors: MERIDIA is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see "**PRECAUTIONS**", Drug Interactions subsection). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA. Similarly, there should be at least a 2-week interval after stopping MERIDIA before starting treatment with MAOIs.

Concomitant Cardiovascular Disease: Treatment with MERIDIA has been associated with increases in heart rate and/or blood pressure. Therefore, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Glaucoma: Because MERIDIA can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

Miscellaneous: Organic causes of obesity (e.g., untreated hypothyroidism) should be excluded before prescribing MERIDIA.

PRECAUTIONS: Pulmonary Hypertension: Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with MERIDIA® (sibutramine hydrochloride monohydrate) Capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not MERIDIA may cause this disease.

Seizures: During premarketing testing, seizures were reported in <0.1% of MERIDIA treated patients. MERIDIA should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Gallstones: Weight loss can precipitate or exacerbate gallstone formation.

Renal/Hepatic Dysfunction: Patients with severe renal impairment or severe hepatic dysfunction have not been systematically studied; MERIDIA should therefore not be used in such patients.

Interference With Cognitive and Motor Performance: Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

Information For Patients: Physicians should instruct their patients to read the patient package insert before starting therapy with MERIDIA and to reread it each time the prescription is renewed.

Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.

Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan (Imitrex®), or tryptophan, since there is a potential for interactions.

Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

Drug Interactions: ***CNS Active Drugs:*** The use of MERIDIA in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of MERIDIA with other centrally-acting drugs is indicated (see "**CONTRAINDICATIONS**" and "**WARNINGS**").

In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, selegiline) in combination with serotonergic agents (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because MERIDIA inhibits serotonin reuptake, MERIDIA should not be used concomitantly with a MAOI (see "**CONTRAINDICATIONS**"). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA. Similarly, at least 2 weeks should elapse between discontinuation of MERIDIA and initiation of treatment with a MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because MERIDIA inhibits serotonin reuptake, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

Drugs That May Raise Blood Pressure and/or Heart Rate: Concomitant use of MERIDIA and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.

Drugs That Inhibit Cytochrome P450($3A_4$) Metabolism: In vitro studies indicated that the cytochrome P450($3A_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The potential for such interactions is described below.

Ketoconazole: Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

Cimetidine: Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.

Alcohol: In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.

Oral Contraceptives: The suppression of ovulation by oral contraceptives was not inhibited by MERIDIA. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

Drugs Highly Bound to Plasma Proteins: Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenicity:*** Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.375 and 15.75 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

Mutagenicity: Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

Impairment of Fertility: In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 32.25 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

Pregnancy: ***Teratogenic Effects - Pregnancy Category C:*** Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32.25 times those following human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

No adequate and well controlled studies with MERIDIA have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing Mothers: It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatric Use: The safety and effectiveness of MERIDIA in pediatric patients under 16 years of age have not been established.

Geriatric Use: Clinical studies of MERIDIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: In placebo-controlled studies, 9% of patients treated with MERIDIA (n = 2068) and 7% of patients treated with placebo (n = 884) withdrew for adverse events.

In placebo-controlled studies, the most common events were dry mouth, anorexia, insomnia, constipation and headache. Adverse events in these studies occurring in ≥1% of MERIDIA treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
BODY SYSTEM	MERIDIA® (n = 2068)	Placebo (n = 884)
Adverse Event	% Incidence	% Incidence
BODY AS A WHOLE		
Headache	30.3	18.6
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthenia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.6
RESPIRATORY SYSTEM		
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough increase	3.8	3.3
Laryngitis	1.3	0.9
SKIN & APPENDAGES		
Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8
SPECIAL SENSES		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
UROGENITAL SYSTEM		
Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal monilia	1.2	0.5
Metrorrhagia	1.0	0.8

The following additional adverse events were reported in ≥1% of all patients who received MERIDIA in controlled and uncontrolled pre-marketing studies.

Body as a Whole: fever.

Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.

Metabolic and Nutritional: peripheral edema.

Musculoskeletal System: arthritis.

Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.

Respiratory System: bronchitis, dyspnea.

Skin and Appendages: pruritus.

Special Senses: amblyopia.

Urogenital System: menstrual disorder.

Postmarketing Reports: Voluntary reports of adverse events temporally associated with the use of MERIDIA are listed below. It is important to emphasize that although these events occurred during treatment with MERIDIA, they may have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events.

abnormal dreams, abnormal ejaculation, abnormal gait, abnormal vision, alopecia, amnesia, anaphylactic shock, anaphylactoid reaction, anemia, anger, angina pectoris, arthrosis, atrial fibrillation, blurred vision, bursitis, cerebrovascular accident, chest pressure, chest tightness, cholecystitis, cholelithiasis, concentration impaired, confusion, congestive heart failure, depression aggravated, dermatitis, dry eye, duodenal ulcer, epistaxis, eructation, eye pain, facial edema, gastrointestinal hemorrhage, Gilles de la Tourette's syndrome, goiter, heart arrest, heart rate decreased, hematuria, hyperglycemia, hyperthyroidism, hypesthesia, hypoglycemia, hypothyroidism, impotence, increased intraocular pressure, increased salivation, increased urinary frequency, intestinal obstruction, leukopenia, libido decreased, libido increased, limb pain, lymphadenopathy, manic reaction, micturition difficulty, mood changes, mouth ulcer, myocardial infarction, nasal congestion, nightmares, otitis externa, otitis media, petechiae, photosensitivity (eyes), photosensitivity (skin), respiratory disorder, serotonin syndrome, short term memory loss, speech disorder, stomach ulcer, sudden unexplained death, supraventricular tachycardia, syncope, thrombocytopenia, tinnitus, tongue edema, torsade de pointes, transient ischemic attack, tremor, twitch, urticaria, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation, vertigo, yawn.

Other Notable Adverse Events: ***Seizures:*** Convulsions were reported as an adverse event in three of 2068 (0.1%) MERIDIA treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the three patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; one had a subsequent diagnosis of brain tumor). The incidence in all subjects who received MERIDIA (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of MERIDIA treated patients and in 0.2% of placebo-treated patients in pre-marketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. MERIDIA may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in one obese patient receiving MERIDIA during pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphatase and bilirubin, were reported as adverse events in 1.6% of MERIDIA-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥2 mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥3x upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the MERIDIA treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

DRUG ABUSE AND DEPENDENCE: Controlled Substance: MERIDIA is controlled in Schedule IV of the Controlled Substances Act (CSA).

Abuse and Physical and Psychological Dependence: Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE: Human Experience: Three cases of overdose have been reported with MERIDIA. The first was in a 2-year-old child of one patient who ingested up to eight 10 mg capsules. No complications were observed during the overnight hospitalization, and the child was discharged the following day with no sequela. The second report was in a 30-year-old male in a depression study who ingested approximately 100 mg of sibutramine in an attempt to commit suicide. The patient suffered no adverse effects or ECG abnormalities post-ingestion. The third report was in the 45-year-old husband of a patient in an obese dyslipidemic study. He ingested 400 mg of his wife's drug supply and was hospitalized for observation; a heart rate of 120 bpm was noted. He was discharged the next day with no apparent sequelae.

Overdose Management: There is no specific antidote to MERIDIA. Treatment should consist of general measures employed in the management of overdosage: an airway should be established; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. The benefits of forced diuresis and hemodialysis are unknown.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by BASF Corporation, Mount Olive, NJ 07828, U.S.A.

IMITREX is a registered trademark of Glaxo Group Limited.

Sibutramine is covered by US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.

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tom ____ mmHg (indicate compression)

*The mean compression for an average ankle size.

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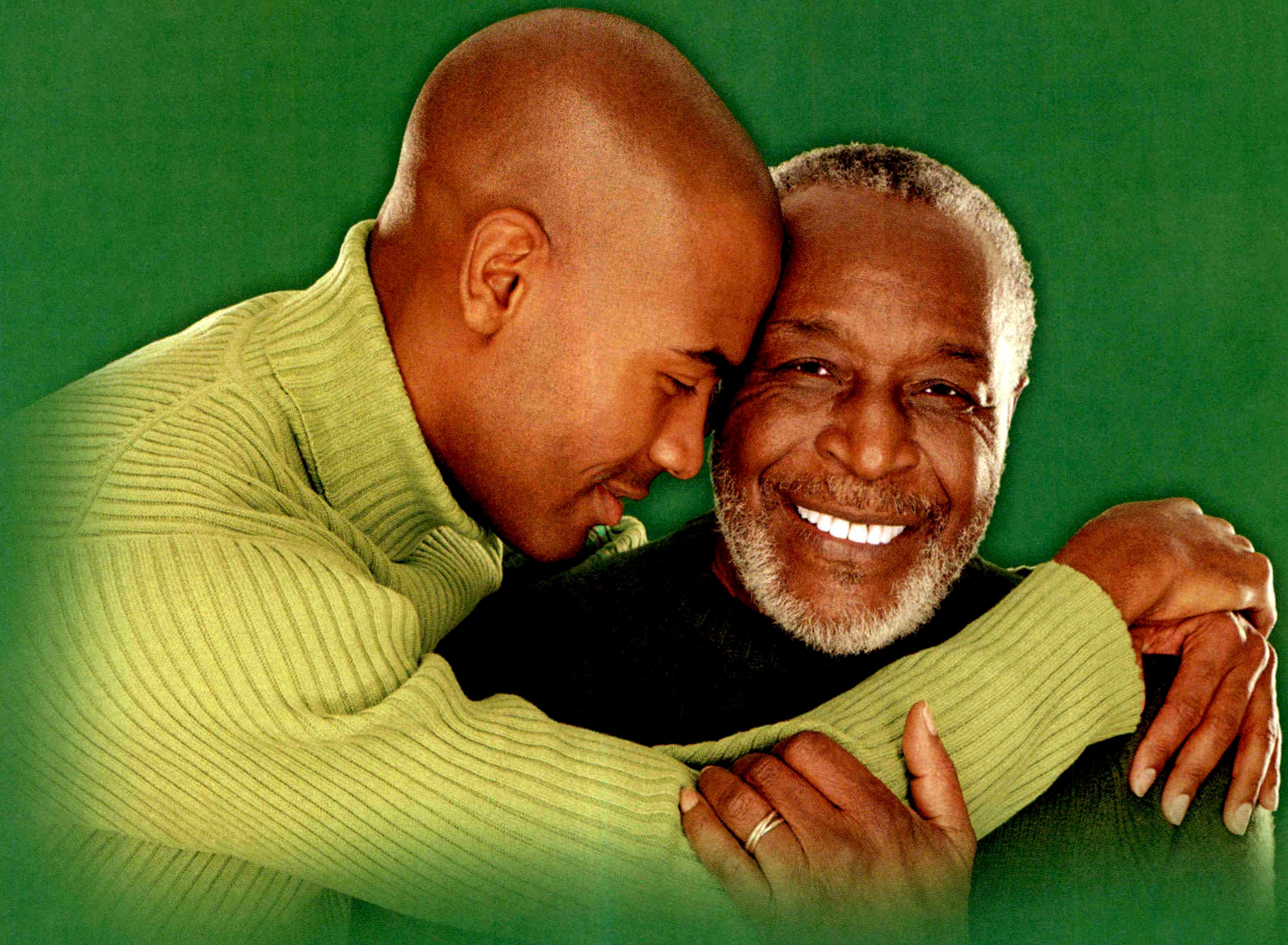

Important clinical considerations

Cardiac considerations: In clinical trials, an increased incidence of heart failure and other cardiovascular events was seen with *Avandia* in combination with insulin, including some patients not known to have prior CHF or pre-existing cardiac conditions. *Avandia* is not indicated for use in combination with insulin.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not recommended in these patients.

Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs.

Hepatic considerations: Liver enzyme monitoring is recommended prior to initiation of *Avandia*, every 2 months for the first 12 months, and periodically thereafter. *Avandia* should not be initiated in patients with clinical evidence of active liver disease or ALT >2.5X the upper limit of normal.

Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received in postmarketing experience. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Over 2.5 million patients...Over 2 years on the market*

insulin-sensitizing AVANDIA®

A potent insulin sensitizer

- Directly targets insulin resistance

Durable glycemic control

- As initial therapy
- In combination with metformin[†] or sulfonylureas[‡1]

#1 prescribed TZD*

- Experience you can count on
- Over 14 million Rxs with over 2.5 million patients*
- Over 2 years on the market*

* Based on overall physician population, Scott-Levin SPA, November 2001; NDC, November 2001, plus nonretail.

[†] Patients who received *Avandia* 8 mg qd or *Avandia* 4 mg bid plus 2.5 g/day of metformin for at least 24 months during 2 double-blind, placebo-controlled studies and their 1 open-label extension.

[‡] Patients who received *Avandia* 2 mg bid plus glyburide for at least 24 months during a double-blind, 26-week study and its open-label extension.

Reference:
1. Data on file, GlaxoSmithKline.

Please see brief summary of prescribing information on the last page of this advertisement.

Other considerations: *Hypoglycemia*—Patients receiving *Avandia* in combination with other hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. *Edema—Avandia* should be used with caution in patients with edema. *Weight gain*—Dose-related weight gain was seen with *Avandia*. *Anemia*—In clinical trials, the frequency of anemia was greater with the combination of *Avandia* plus metformin compared to metformin alone. Lower pretreatment hemoglobin/hematocrit levels may have contributed to this higher reporting rate.

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Insulin-sensitizing
Avandia®
rosiglitazone maleate

The future of type 2 diabetes therapy is NOW.

#1 Prescribed TZD...Over 14 million Rxs...Over 2.5 million patients...Over 2 years on the market*

AVANDIA® rosiglitazone maleate tablets

Before prescribing, see complete prescribing information. The following is a brief summary.

INDICATIONS AND USAGE: *Avandia* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. *Avandia* is indicated as monotherapy. *Avandia* is also indicated for use in combination with a sulfonylurea or metformin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, *Avandia* should be added to, rather than substituted for, a sulfonylurea or metformin. Prior to initiation of therapy with *Avandia*, investigate and treat secondary causes of poor glycemic control, e.g., infection.

CONTRAINDICATIONS: *Avandia* is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS: Cardiac Failure and Other Cardiac Effects: *Avandia*, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not recommended in patients with NYHA Class 3 and 4 cardiac status. In two 26-week U.S. trials involving 611 patients with type 2 diabetes, *Avandia* plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on *Avandia* and insulin combination therapy compared to insulin and placebo. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of *Avandia*. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double blind part of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. **The use of *Avandia* in combination therapy with insulin is not indicated (see ADVERSE REACTIONS).**

PRECAUTIONS: General: Due to its mechanism of action, *Avandia* is active only in the presence of endogenous insulin. Therefore, *Avandia* should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ***Hypoglycemia:*** Patients receiving *Avandia* in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary. ***Edema:*** *Avandia* should be used with caution in patients with edema. In a clinical study in healthy volunteers who received *Avandia* 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, *Avandia* should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients). In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia*, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia* (see ADVERSE REACTIONS).

Weight Gain: Dose-related weight gain was seen with *Avandia* alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 1. Weight Changes (kg) from Baseline During Clinical Trials with *Avandia*

		Control Group		***Avandia* 4 mg**	***Avandia* 8 mg**
Monotherapy	**Duration**		**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**
	26 weeks	placebo	-0.9 (-2.8, 0.9)	1.0 (-0.9, 3.6)	3.1 (1.1, 5.8)
	52 weeks	sulfonylurea	2.0 (0, 4.0)	2.0 (-0.6, 4.0)	2.6 (0, 5.3)
Combination therapy					
sulfonylurea	26 weeks	sulfonylurea	0 (-1.3, 1.2)	1.8 (0, 3.1)	—
metformin	26 weeks	metformin	-1.4 (-3.2, 0.2)	0.8 (-1.0, 2.6)	2.1 (0, 4.3)
insulin	26 weeks	insulin	0.9 (-0.5, 2.7)	4.1 (1.4, 6.3)	5.4 (3.4, 7.3)

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for *Avandia* alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of *Avandia* therapy or following an increase in *Avandia* dose. White blood cell counts also decreased slightly in patients treated with *Avandia*. The observed changes may be related to the increased plasma volume observed with treatment with *Avandia* and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities).

Ovulation: Therapy with *Avandia*, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking *Avandia* (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known. Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with *Avandia* should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3X upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported. In pre-approval clinical studies in 4598 patients treated with *Avandia*, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In pre-approval controlled trials, 0.2% of patients treated with *Avandia* had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with *Avandia* were reversible and were not clearly causally related to therapy with *Avandia*. In postmarketing experience with *Avandia*, reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with *Avandia* undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with *Avandia* in all patients. Therapy with *Avandia* should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with *Avandia*, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with *Avandia* should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with *Avandia* in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X upper limit of normal in patients on therapy with *Avandia*, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with *Avandia* should be discontinued. There are no data available from clinical trials to evaluate the safety of *Avandia* in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. *Avandia* should not be used in patients who experienced jaundice while taking troglitazone. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with *Avandia* should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Laboratory Tests: Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response. Liver enzyme monitoring is recommended prior to initiation of therapy with *Avandia* in all patients and periodically thereafter (see PRECAUTIONS, *Hepatic Effects* and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients: Patients should be informed of the following. It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and every 2 months for the first 12 months, and periodically thereafter. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on *Avandia* should immediately report these symptoms to their physician.

Drug Interactions: Drugs Metabolized by Cytochrome P_{450}: *Avandia* was shown to have no clinically relevant drug interactions with nifedipine and oral contraceptives, which are predominantly metabolized by CYP3A4, glyburide, metformin, acarbose, digoxin, warfarin, ethanol and ranitidine. See full prescribing information.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day, approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy: Pregnancy Category C. There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. *Avandia* should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Labor and Delivery: The effect of rosiglitazone on labor and delivery in humans is not known. **Nursing Mothers:** Drug-related material was detected in milk from lactating rats. It is not known whether *Avandia* is excreted in human milk. Because many drugs are excreted in human milk, *Avandia* should not be administered to a nursing woman.

ADVERSE REACTIONS: In clinical trials, approximately 4600 patients with type 2 diabetes have been treated with *Avandia*; 3300 patients were treated for 6 months or longer and 2000 patients were treated for 12 months or longer.

The following adverse events (occurring at rates ≥5% in any treatment group) were reported by patients in double-blind clinical trials with *Avandia* as monotherapy (N=2526), compared to events seen in patients treated with placebo (N=601), metformin (N=225) or sulfonylureas (N=626), respectively: Upper respiratory tract infection (9.9%, 8.7%, 8.9%, 7.3%); injury (7.6%, 4.3%, 7.6%, 6.1%); headache (5.9%, 5.0%, 8.9%, 5.4%); back pain (4.0%, 3.8%, 4.0%, 5.0%); hyperglycemia (3.9%, 5.7%, 4.4%, 8.1%); fatigue (3.6%, 5.0%, 4.0%, 1.9%); sinusitis (3.2%, 4.5%, 5.3%, 3.0%); diarrhea (2.3%, 3.3%, 15.6%, 3.0%), and hypoglycemia (0.6%, 0.2%, 1.3%, 5.9%). The sulfonylurea group includes patients receiving glyburide (N=514), gliclazide (N=91) or glipizide (N=21).

A small number of patients treated with *Avandia* had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with *Avandia*. In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Edema was reported in 4.8% of patients receiving *Avandia* compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when *Avandia* was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with *Avandia*. Reports of anemia (7.1%) were greater in patients treated with a combination of *Avandia* and metformin compared to monotherapy with *Avandia* or in combination with a sulfonylurea. Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic). In 26-week double-blind studies, edema was reported with higher frequency in the *Avandia* plus insulin combination trials (insulin, 5.4%, and *Avandia* in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with *Avandia* (see WARNINGS, Cardiac Failure and Other Cardiac Effects). In postmarketing experience with *Avandia*, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported.

Laboratory Abnormalities: Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with *Avandia* (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of *Avandia* and other hypoglycemic agents or *Avandia* monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients treated with *Avandia*. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with *Avandia*. **Lipids:** Changes in serum lipids have been observed following treatment with *Avandia* (see CLINICAL STUDIES in the full prescribing information).

Serum Transaminase Levels: In clinical studies in 4598 patients treated with *Avandia* encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels. In controlled trials, 0.2% of patients treated with *Avandia* had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with *Avandia* compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with *Avandia*, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with *Avandia*, reports of hepatic enzyme elevations three or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, *Hepatic Effects*).

DOSAGE AND ADMINISTRATION: The management of antidiabetic therapy should be individualized. *Avandia* may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as indicated below. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES in the full prescribing information. *Avandia* may be taken with or without food. **Monotherapy:** The usual starting dose of *Avandia* is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c. **Combination Therapy with a Sulfonylurea or Metformin:** When *Avandia* is added to existing therapy, the current dose of sulfonylurea or metformin can be continued upon initiation of *Avandia* therapy. **Sulfonylurea:** When used in combination with sulfonylurea, the recommended dose of *Avandia* is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. **Metformin:** The usual starting dose of *Avandia* in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with *Avandia*. **Maximum Recommended Dose:** The dose of *Avandia* should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin. Doses of *Avandia* greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials. *Avandia* may be taken with or without food. No dosage adjustments are required for the elderly. No dosage adjustment is necessary when *Avandia* is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and *Avandia* is also contraindicated in patients with renal impairment. Therapy with *Avandia* should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Hepatic Impairment in full prescribing information). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with *Avandia* and periodically thereafter (see PRECAUTIONS, *Hepatic Effects*). There are no data on the use of *Avandia* in patients under 18 years of age; therefore, use of *Avandia* in pediatric patients is not recommended.

BRS-AV:L7

Rx only

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*Based on overall physician population, Scott-Levin SPA, November 2001; NDC, November 2001, plus nonretail.

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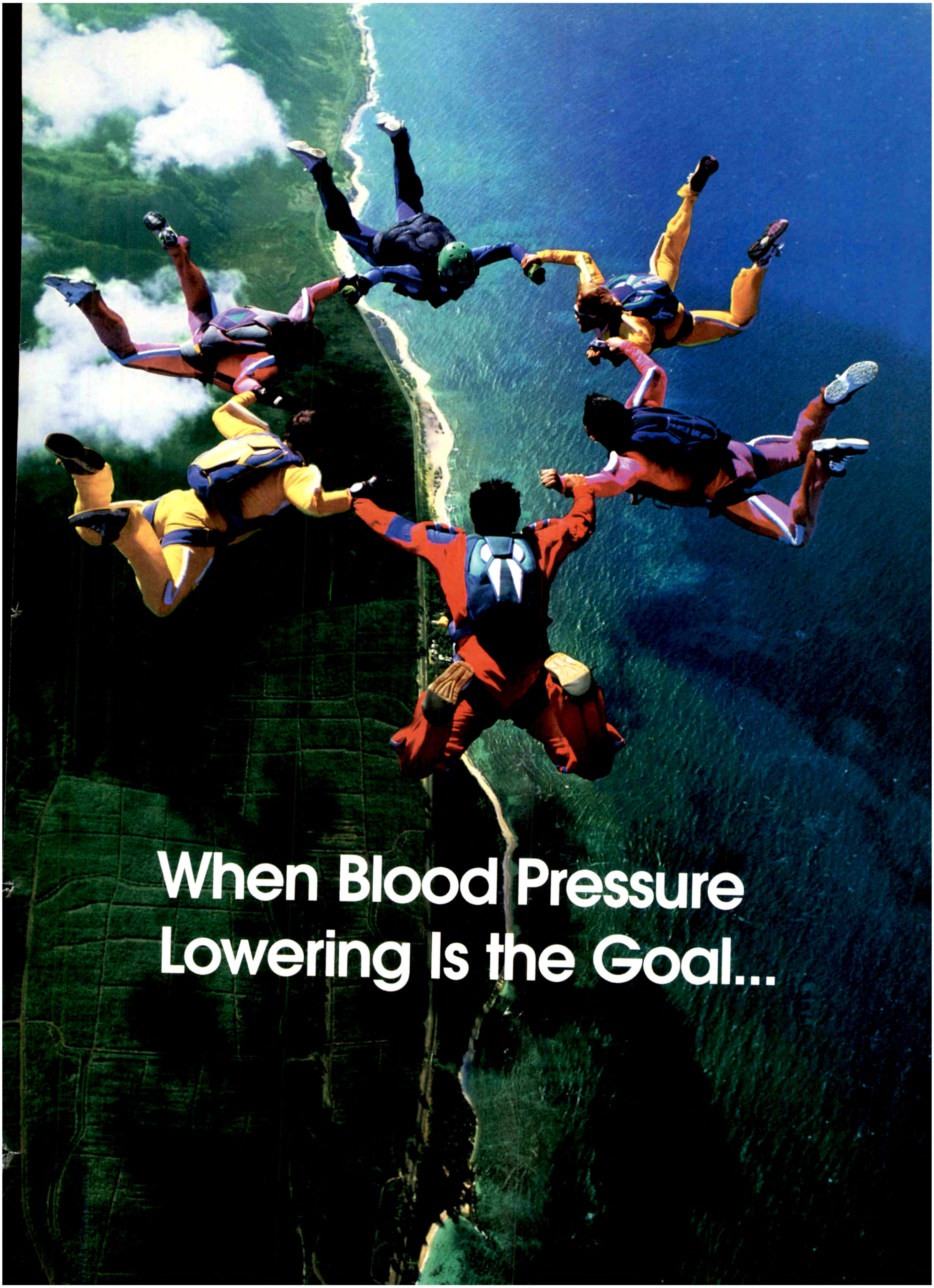
When Blood Pressure Lowering Is the Goal...

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, BENICAR should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality** in the prescribing information.

the Possibilities...

See what the new ARB—BENICAR—can do!

Significant reductions at 20 mg QD starting dose

- Demonstrated in multiple placebo-controlled studies in over 2500 patients with essential hypertension

Complete QD coverage

- Efficacy maintained throughout crucial early morning period[1]

Favorable safety and tolerability

- Incidence of adverse events (AEs) similar to placebo

The only AE that occurred in >1% of patients treated with BENICAR and more frequently than placebo was dizziness (3% vs 1%).

BENICAR is first-line therapy indicated for the treatment of hypertension.
It may be used alone or in combination with other antihypertensive agents.

NEW

TABLETS

Benicar™

(olmesartan medoxomil)

Please see brief summary of prescribing information on adjacent page

BENICAR™* Tablets
(olmesartan medoxomil)

Brief Summary—See package insert for full prescribing information.

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, BENICAR™ should be discontinued as soon as possible. **See WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

INDICATIONS AND USAGE
BENICAR™ is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS
BENICAR™ is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS
Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, BENICAR™ should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of BENICAR™ as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, BENICAR™ should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of BENICAR™ in pregnant women. No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose [MRHD] of olmesartan medoxomil on a mg/m^2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 basis; higher doses could not be evaluated for effects on fetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses of ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

Hypotension in Volume- or Salt-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with BENICAR™. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. (See **DOSAGE AND ADMINISTRATION** section of full prescribing information.) A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS
General
Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil. (See **CLINICAL PHARMACOLOGY, Special Populations** section of full prescribing information.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions
No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3/Mg(OH)_2$]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on an mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung). Olmesartan medoxomil also tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay (olmesartan not tested). Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney, for DNA damage in the rat kidney (comet assay) and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters). See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

Nursing Mothers
It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Of the total number of hypertensive patients receiving BENICAR™ in clinical studies, more than 20% were 65 years of age and over, while more than 5% were 75 years of age and older. No overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
BENICAR™ has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year. Treatment with BENICAR™ was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil.

The overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 32/1179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence versus placebo was dizziness (3% vs. 1%).

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with olmesartan medoxomil, but also occurred at about the same or greater incidence in patients receiving placebo: back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, inflicted injury, influenza-like symptoms, pharyngitis, rhinitis, sinusitis and upper respiratory tract infection.

The incidence of cough was similar in placebo (0.7%) and BENICAR™ (0.9%) patients.

Other (potentially important) adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in the more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are listed below.

Body as a Whole: chest pain, fatigue, pain, peripheral edema
Central and Peripheral Nervous System: vertigo
Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, nausea
Heart Rate and Rhythm Disorders: tachycardia
Metabolic and Nutritional Disorders: hypercholesterolemia, hyperlipemia, hyperuricemia
Musculoskeletal: arthralgia, arthritis, myalgia, skeletal pain
Psychiatric Disorders: insomnia
Skin and Appendages: rash
Urinary System: urinary tract infection

Facial edema was reported in 5 patients receiving olmesartan medoxomil. Angioedema has been reported with other angiotensin II antagonists.

Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dL and 0.3 volume percent, respectively) were observed.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients (0.1%) assigned to olmesartan medoxomil and one patient (0.2%) assigned to placebo in clinical trials were withdrawn because of abnormal liver chemistries (transaminases or total bilirubin). Of the five olmesartan medoxomil patients, three had elevated transaminases, which were attributed to alcohol use, and one had a single elevated bilirubin value, which normalized while treatment continued.

OVERDOSAGE
Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialyzability of olmesartan is unknown.

No lethality was observed in acute toxicity studies in mice and rats given single oral doses up to 2000 mg/kg of olmesartan medoxomil. The minimum lethal oral dose of olmesartan medoxomil in dogs was greater than 1500 mg/kg.

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Reference: 1. Neutel JM. Clinical studies of CS-866, the newest angiotensin II receptor antagonist. *Am J Cardiol.* 2001;87(suppl):37C-43C.

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Screening for Colorectal Cancer: Recommendations from the United States Preventive Services Task Force

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The full reports are titled "Cost-Effectiveness Analyses of Colorectal Cancer Screening: A Systematic Review for the U.S. Preventive Services Task Force," "Screening for Colorectal Cancer: Recommendation and Rationale," and "Screening for Colorectal Cancer in Adults at Average Risk: A Summary of the Evidence for the U.S. Preventive Services Task Force." They are in the 16 July 2002 issue of *Annals of Internal Medicine* (volume 137, pages 96-104, 129-131, and 132-141). The first report was written by M Pignone, S Saha, T Hoerger, and J Mandelblatt; the second report was written by the U.S. Preventive Services Task Force; and the third report was written by M Pignone, M Rich, SM Teutsch, AO Berg, and KN Lohr.

What is the United States Preventive Services Task Force?

The United States Preventive Services Task Force (USPSTF) is a group of physicians and health care experts that reviews published research and makes recommendations about preventive health care.

What is the problem and what is known about it so far?

Colorectal cancer is one of the most common types of cancer. Screening prevents colorectal cancer deaths by 1) finding and removing noncancerous outgrowths of the colon or rectum (polyps) before they become cancer and 2) finding cancer at early, curable stages. Available screening tests include fecal occult blood testing (FOBT), sigmoidoscopy, colonoscopy, and barium enema. Fecal occult blood testing uses a chemical reaction to find traces of blood in stool. Polyps and cancer can cause blood to leak into the stool, so a positive result on FOBT suggests the need for further testing. Sigmoidoscopy involves looking into the rectum and lower colon through a flexible tube-shaped instrument; colonoscopy uses a similar but longer instrument to look at the entire length of the colon. Doctors can take samples of the colon (biopsies) and remove polyps during both procedures. Barium enema involves taking x-rays of the abdomen after putting barium (a material that appears white on x-ray) into a person's colon by enema. If x-rays indicate a lesion in the colon, follow-up testing with colonoscopy is needed. Fecal occult blood testing is inexpensive, colonoscopy is expensive, and sigmoidoscopy and barium enema are moderately priced.

How did the USPSTF develop these recommendations?

The USPSTF reviewed published research to evaluate the benefits, harms, and costs of screening for colorectal cancer.

What did the authors find?

Several high-quality studies show that FOBT helps to decrease colorectal cancer deaths by up to one third among adults over age 50. Studies showing the effectiveness of sigmoidoscopy and colonoscopy are of lower quality but also show benefits. Barium enema can also detect polyps and cancer, but the effect of barium enema on deaths from colorectal cancer is unknown. Existing studies are unable to tell us which test is best. The seven studies of the cost-effectiveness of colorectal cancer screening found all tests to be cost-effective but could not identify a single best strategy or determine the best age to start and stop screening.

What does the USPSTF suggest that patients do?

The USPSTF strongly recommends that adults begin screening for colorectal cancer at age 50, the age at which risk starts to increase in the general population. The best options for screening include FOBT, sigmoidoscopy (alone or with FOBT), or colonoscopy. Barium enema is also an option, but it is less accurate than colonoscopy and its effects on colorectal cancer deaths are unknown. The Task Force did not recommend a specific screening test.

Patients should discuss the advantages and disadvantages of the various colorectal cancer screening tests with their doctors to decide which test is best for them. The frequency of screening depends on the test a patient uses: every 1 to 2 years for FOBT, every 5 years for sigmoidoscopy and barium enema, and every 10 years for colonoscopy.

What are the cautions related to these recommendations?

These recommendations do not apply to people who have a family history or a personal history that puts them at high risk for colorectal cancer. As better studies become available, the USPSTF may modify these recommendations.

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AcipHex®
rabeprazole sodium
20-MG TABLETS

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX® is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX® is indicated for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg•hr/mL which is 1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 μg•hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μg•hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μg•hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPR T) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/−) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ^{14}C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m^2) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in ≤1/1000 patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. Rare: abdomen enlarged, face edema, hangover effect. *Cardiovascular System:* hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. Rare: bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTC prolongation and ventricular tachycardia. *Digestive System:* diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. Rare: bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. *Endocrine System:* hyperthyroidism, hypothyroidism. *Hemic & Lymphatic System:* anemia, ecchymosis, lymphadenopathy, hypochromic anemia. *Metabolic & Nutritional Disorders:* peripheral edema, edema, weight gain, gout, dehydration, weight loss. *Musculo-Skeletal System:* myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. Rare: twitching. *Nervous System:* insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertonia, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. Rare: agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. *Respiratory System:* dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. Rare: apnea, hypoventilation. *Skin and Appendages:* rash, pruritus, sweating, urticaria, alopecia. Rare: dry skin, herpes zoster, psoriasis, skin discoloration. *Special Senses:* cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. Rare: corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. *Urogenital System:* cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. Rare: breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

AXPI-28 200192

References:

1. Robinson M, Fitzgerald S, Hegedus R, Murthy A, Jokubaitis L, on behalf of the F.A.S.T. trial investigators. Onset of symptom relief with rabeprazole: a community-based, open-label assessment of patients with erosive oesophagitis. *Aliment Pharmacol Ther.* 2002;16:445-454. **2.** Pantoflickova D, Dorta G, Jornod P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs [abstract]. *Gastroenterology.* 2000;118:A5895.

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IN EROSIVE GERD

HIT HEARTBURN HARD

ACIPHEX®— 24-hour acid control from the first dose

- Symptom relief on day 1*[1]
- All-day, all-night acid control[2]
- An excellent safety profile

In clinical trials the most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

*Erosive GERD patients with moderate to severe symptoms at baseline who achieved mild or no symptoms during treatment in a large, open-label, multicenter study (n=1449 daytime; n=1469 nighttime). Within 36 hours of the initial visit, patients began reporting the severity of their symptoms, including daytime and nighttime heartburn, for the first 7 days and on day 28.

Please see brief summary of prescribing information on adjacent page.

ONCE-A-DAY

AcipHex®

rabeprazole sodium

20-MG TABLETS

24-hour acid control from the first dose

Annals of Internal Medicine

ARTICLE

Ciprofloxacin plus Piperacillin Compared with Tobramycin plus Piperacillin as Empirical Therapy in Febrile Neutropenic Patients

A Randomized, Double-Blind Trial

James E. Peacock Jr., MD; Deirdre A. Herrington, MD; James C. Wade, MD; Hillard M. Lazarus, MD; Michael D. Reed, MD; Jane W. Sinclair, RN; Daniel C. Haverstock, MS; Steven F. Kowalsky, PharmD; David D. Hurd, MD; Deborah A. Cushing, RN; Colleen P. Harman, RN; and Gerald R. Donowitz, MD

Background: **Therapy with an aminoglycoside and a β-lactam remains common empirical therapy for febrile neutropenic patients. Concerns of aminoglycoside-induced ototoxicity and nephrotoxicity have led to studies of alternate regimens.**

Objective: **To determine whether ciprofloxacin–piperacillin is equivalent to tobramycin–piperacillin as empirical therapy for neutropenic fever.**

Design: **Randomized, double-blind multicenter trial.**

Setting: **Seven U.S. university-affiliated hospitals and one private research center.**

Patients: **Febrile (temperature ≥ 38 °C), neutropenic (neutrophil level $< 1 \times 10^9$ cells/L) hospitalized patients who had leukemia, lymphoma, or solid tumors, or were undergoing bone marrow transplantation.**

Interventions: **Patients received piperacillin, 50 mg/kg of body weight intravenously every 4 hours, and ciprofloxacin, 400 mg intravenously every 8 hours, or tobramycin, 2 mg/kg intravenously every 8 hours.**

Measurements: **Success was defined as resolution of infection and previously positive cultures without the need to give additional antimicrobial agents.**

Results: **543 febrile episodes were evaluated, of which 471 were clinically evaluable (234 in the ciprofloxacin–piperacillin group and 237 in the tobramycin–piperacillin group). Success rates in the ciprofloxacin–piperacillin group (63 of 234 febrile episodes) and tobramycin–piperacillin group (52 of 237 episodes) were similar (27% vs. 22%, respectively; difference, 5.0 percentage points [95% CI, −2.3 to 12.8 percentage points]), as was survival (96.2% of patients receiving ciprofloxacin–piperacillin versus 94.1% of patients receiving tobramycin–piperacillin; difference, 2.1 percentage points [CI, −2.2 to 6.4 percentage points]). Additions to the initial antimicrobial regimen were the most common reason for treatment failure in both groups (accounting for 67% of failures in the ciprofloxacin–piperacillin group and 72% in the tobramycin–piperacillin group; difference, 5.0 percentage points [CI, −13.8 to 3.7 percentage points]). Fevers resolved faster in patients receiving ciprofloxacin–piperacillin than in patients receiving tobramycin–piperacillin (mean, 5 vs. 6 days) ($P = 0.005$). No significant differences in adverse events or toxicity were noted ($P = 0.083$).**

Conclusion: **Ciprofloxacin–piperacillin is as safe and effective as tobramycin–piperacillin for empirical therapy of neutropenic fever.**

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For author affiliations, see end of text.

See editorial comment on pp 123-124.

Empirical therapy with antibiotic combinations aimed at gram-negative bacilli has been used in febrile neutropenic patients for more than 30 years (1). Aminoglycosides have remained an essential component of this combination therapy, although gram-positive organisms have emerged as major sources of infection (2–6). Ongoing concerns about aminoglycoside-induced ototoxicity and nephrotoxicity and the need for monitoring of serum drug levels have led to studies of other potentially useful agents.

Ciprofloxacin is one of the most potent of the presently available quinolones against *Pseudomonas aeruginosa*; has excellent activity against most *Enterobacteriaceae*; and provides coverage against many strains of *Staphylococcus aureus*, coagulase-negative staphylococci, and some strains of streptococci. Synergy with β-lactams against some strains of gram-negative bacilli has been demonstrated (7–11). Ciprofloxacin has been used as part of combination therapy, as modified monotherapy, and as true monotherapy in febrile neutropenic patients (12–22). Unfortunately, previous studies have involved relatively small numbers of patients and heterogeneous populations; thus, no clear conclusions have been drawn about efficacy. Therefore, we undertook a randomized, double-blind study to determine whether ciprofloxacin was equivalent to tobramycin when used as part of combination therapy with piperacillin as empirical therapy for neutropenic fever.

METHODS

Patients

The study groups were hospitalized patients with cancer and granulocytopenia (absolute granulocyte counts $< 1 \times 10^9$ cells/L within 24 hours of study onset). The patients were 16 years of age or older and required antibiotic therapy for fever and presumed infection (a clinically documented infection defined by signs and symptoms compatible with infection in the presence or absence of fever or a microbiologically documented infection with or without fever). Fever was defined as an oral temperature of at least 38 °C. Patients could be enrolled in the trial more than once as long as each entry represented a different neutropenic episode. Seven university-affiliated hospitals and a private research center (the Scripps Institute in La Jolla, California) participated in this study from June 1992 to July 1995.

We excluded patients with allergy to aminoglycosides,

Context

Hospitalized patients with neutropenia have high risks for opportunistic gram-negative infections.

An aminoglycoside in combination with an antipseudomonas β-lactam, a traditional empirical therapy for febrile neutropenic patients, is limited by potential nephrotoxicity.

Contribution

This large randomized trial showed that ciprofloxacin plus piperacillin and tobramycin plus piperacillin were equally effective empirical therapies for hospitalized patients with fever and neutropenia.

Side effects, including nephrotoxicity, were common with both regimens and did not differ significantly.

Implications

Combination therapy with the β-lactam piperacillin plus a quinolone (ciprofloxacin) or an aminoglycoside (tobramycin) is a viable option for neutropenic febrile patients.

–The Editors

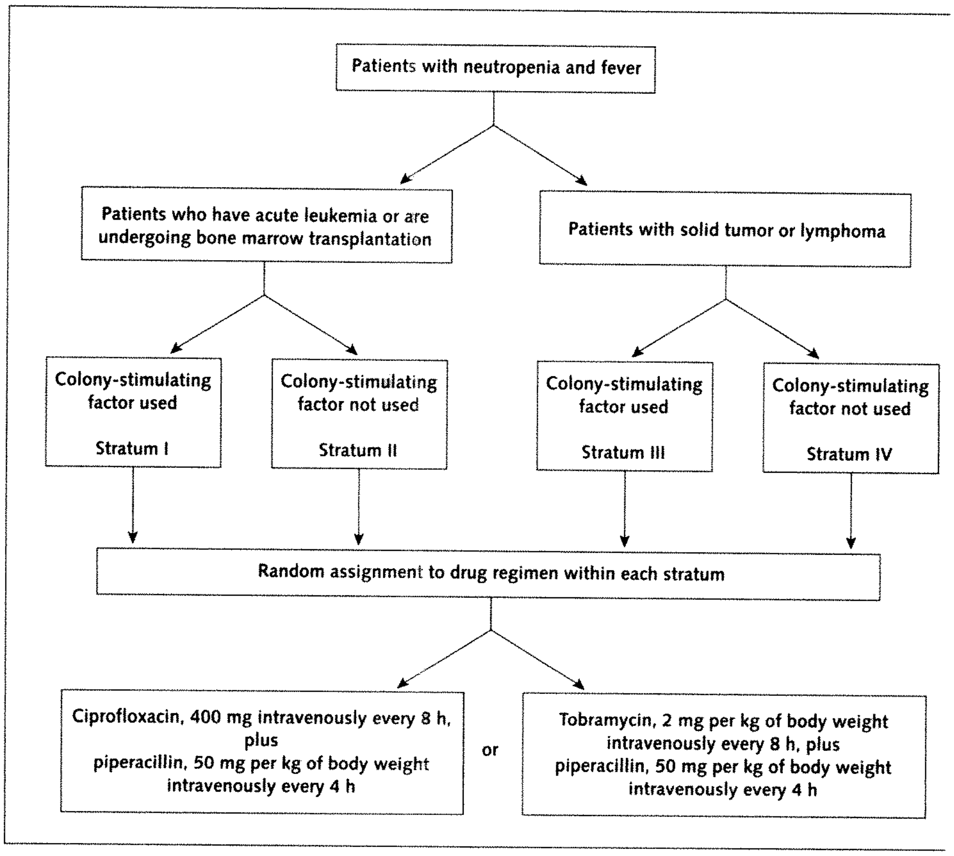
quinolones, or penicillin; infections caused by bacteria presumed to be resistant to the study drugs; high probability of death within 24 hours; or creatinine clearance of 30 mL/min or less. We also excluded those who were pregnant or nursing. Patients receiving any systemic antimicrobial therapy within 7 days before initiation of the study drug were excluded, except the following drugs: antifungal or antiviral agents, trimethoprim–sulfamethoxazole prophylaxis (to be discontinued when the study began), and cefazolin prophylaxis for placement of indwelling venous catheters.

The institutional review boards at each participating center approved the study protocol. Patients or their guardians provided written informed consent to participate in the study.

Random Assignment to Antibiotic Regimen

Randomization was stratified according to the nature of the underlying disease (acute leukemia or bone marrow transplantation vs. lymphoma or solid tumor) and the use of recombinant colony-stimulating factors during the neutropenic episode (**Figure 1**). Patients were randomly assigned to receive piperacillin, 50 mg/kg of body weight intravenously every 4 hours, plus ciprofloxacin, 400 mg intravenously every 8 hours, or tobramycin, 2 mg/kg intravenously every 8 hours. Administration of antibiotics was double-blinded; only the pharmacists dispensing the medication were unblinded. Placebo was administered when necessary to maintain blinding with regard to study drug assignment when renal impairment led to changes in dosing intervals.

Figure 1. **Randomization schema.**


Patients with neutropenia and fever
Patients who have acute leukemia or are undergoing bone marrow transplantation
Patients with solid tumor or lymphoma
Colony-stimulating factor used
Stratum I
Colony-stimulating factor not used
Stratum II
Colony-stimulating factor used
Stratum III
Colony-stimulating factor not used
Stratum IV
Random assignment to drug regimen within each stratum
Ciprofloxacin, 400 mg intravenously every 8 h, plus piperacillin, 50 mg per kg of body weight intravenously every 4 h
or
Tobramycin, 2 mg per kg of body weight intravenously every 8 h, plus piperacillin, 50 mg per kg of body weight intravenously every 4 h

Evaluation and Monitoring

At baseline, we performed cultures, laboratory tests, and radiography on all patients at the onset of fever. When possible, audiometry was performed within 24 hours of starting the study drug and again at the end of therapy. Peak and trough concentrations of serum tobramycin were determined serially in all patients until renal function stabilized. All drug concentrations were reported directly to an unblinded pharmacist who calculated dosages to maintain the 30-minute postdose serum concentration (peak) above 6 μg/mL and the 30-minute predose serum concentration (trough) below 2 μg/mL.

Patients were monitored prospectively for signs of drug toxicity and adverse events. Definitions of expected toxicities were established and included in the protocol before the start of the study. Toxicity was reported to be probably related to antibiotics if it followed a consistent temporal sequence with drug administration, abated after discontinuation of drug use, and was not clearly attributable to other causes. Toxicity was judged to be possibly related to antibiotics if it followed a consistent temporal sequence with drug use but could have been produced by the patient's underlying disease or other drug exposures. For ototoxicity and nephrotoxicity, antibiotic association was judged to be probable if patients had not received other potential toxins and considered possible if other potential toxins were concurrently administered.

Primary Outcome Variable

The primary outcome variable in this study was success or failure of treatment of infection. Patients in the intention-to-treat group and those in the subgroup meeting the criteria for being clinically evaluable were examined. Patients were considered clinically evaluable if they 1) met the inclusion criteria (and did not satisfy the exclusion criteria) and 2) received study drugs for at least 4 days or received study drugs for fewer than 4 days because of treatment failure or an adverse event.

For treatment success, patients had to satisfy all of the following criteria: 1) normal body temperature on 4 consecutive days, 2) eradication of any isolated pathogen from the bloodstream or local site of infection, 3) resolution of clinical signs of infection, and 4) no modification of antimicrobial therapy. Failure was defined as not meeting all of the criteria for success or death from infection.

Secondary Outcome Variables

Secondary outcome variables included survival during the neutropenic period and subsequent infection, superinfection, or relapse. Survival during the neutropenic period was defined as surviving from when the absolute neutrophil count decreased to less than 1×10^9 cells/L until when it reached 0.5×10^9 cells/L or higher. We considered subsequent infection to be an infection at a site other than the primary site of infection occurring more than 72 hours after the patient started taking the study medication. Superinfection was considered a second infection at the initial site caused by an organism other than the initial pathogen and occurring more than 72 hours after the patient started taking the study medication. Relapse was defined as recurrence of an infection at the initial site with the original pathogen.

Statistical Analysis

We estimated that a sample size of 568 episodes was necessary for meaningful evaluation of the primary outcome variable (defined as treatment success). This estimate was based on the goal of demonstrating treatment equivalence, with a Δ of 15% and with the assumption that 50% of patients would have documented infections. Assuming a size per treatment group of 142 patients with documented infections, we estimated that the study would have 80% power to demonstrate equivalence. We used chi-square tests to evaluate for differences between the categorical baseline and medical characteristics of the treatment groups. For continuous baseline variables, we conducted two-way analyses of variance (with one term for study site and one term for treatment).

For the variable of treatment of infection, we constructed a 95% confidence interval around the treatment-group differences for the clinically evaluable patients and the intention-to-treat patients. We used a Mantel–Haenszel weighting scheme for this interval, in which the weights were the sample sizes from each participating center. Four of the eight centers each enrolled at least 113 patients, while the other four centers each enrolled 17 or fewer patients. To avoid possible nonrepresentation of a treatment group in the confidence interval construction, we pooled the four small centers while the study was still blinded and treated them as one center. Centers were pooled only for the confidence interval for the treatment-of-infection variable; this was justified by the similarity of results between small and large centers.

We used Kaplan–Meier curves to estimate the distribution of time to fever response by using a Wilcoxon rank-sum test to determine whether the curves differed significantly. Chi-square tests were used to evaluate for differences between treatment groups in incidence of adverse events. We planned additional safety and efficacy analyses to account for the re-entry of the same patient into the study for multiple independent neutropenic episodes. We used only the first course of therapy for each patient. Confidence intervals for demographic variables and secondary efficacy variables were generated by using a normal approximation to the binomial distribution, with a continuity correction.

Role of the Funding Source

Bayer Corp., Pharmaceutical Division, reviewed the data for accuracy (compared with source documents) and provided statistical analysis. Interpretation of results and decisions about publication were left to the principal investigators.

Table 1. **Patient Demographic and Baseline Medical Characteristics***

Characteristic	Ciprofloxacin–Piperacillin Group (n = 271)	Tobramycin–Piperacillin Group (n = 269)	*P* Value
Mean age (range), *y*	48.6 (19–84)	49.6 (18–81)	>0.2†
Sex, %			>0.2‡
Male	131 (48.3)	140 (52.0)	
Female	140 (51.7)	129 (48.0)	
Underlying disease, %			>0.2‡
Acute leukemia	83 (30.6)	90 (33.4)	
Bone marrow transplant	93 (34.3)	79 (29.4)	
Lymphoma	29 (10.7)	33 (12.3)	
Solid tumor	49 (18.1)	53 (19.7)	
Other	17 (6.3)	14 (5.2)	
Use of growth factors, %	103 (44)	107 (45)	>0.2
Neutrophil count at start of study, %§			>0.2‡
$<0.1 \times 10^9$ cells/L	79 (29.2)	72 (26.8)	
0.1 to 0.499×10^9 cells/L	157 (57.9)	160 (59.4)	
0.5 to 1×10^9 cells/L	21 (8)	29 (11)	
Mean duration of granulocytopenia, *d*	16.6	16.9	>0.2†
Mean duration of study drug therapy, *d*	9.9	9.2	0.2†

* Intention-to-treat population (3 patients who did not receive study drug were excluded from analysis).

† Continuous variables analyzed via two-way analysis of variance.

‡ Categorical variables analyzed by performing a chi-square test.

§ The percentages do not add to 100%. Patients not accounted for are those with an absolute neutrophil count greater than 1×10^9 cells/L at the start of the study whose absolute neutrophil count decreased below 1×10^9 cells/L within 24 h of starting the study.

RESULTS

We studied a total of 543 febrile episodes in 485 patients: 271 episodes in the ciprofloxacin–piperacillin group and 272 in the tobramycin–piperacillin group (**Table 1**). Patients who had acute leukemia or who underwent bone marrow transplantation accounted for most patients in each treatment group. We noted no significant differences among the numbers of patients enrolled in the strata ($P >$ 0.2). Growth factors were used in 44% of patient-episodes in the ciprofloxacin–piperacillin group and 45% of patient-episodes in the tobramycin–piperacillin group (difference, −1 percentage point [95% CI, −10.2 to 7.3 percentage points]). Forty-eight patients were enrolled in the study more than once. Two weeks was the shortest interval between study re-entry. All patients except three, none of whom received study medication, were included in the intention-to-treat analysis.

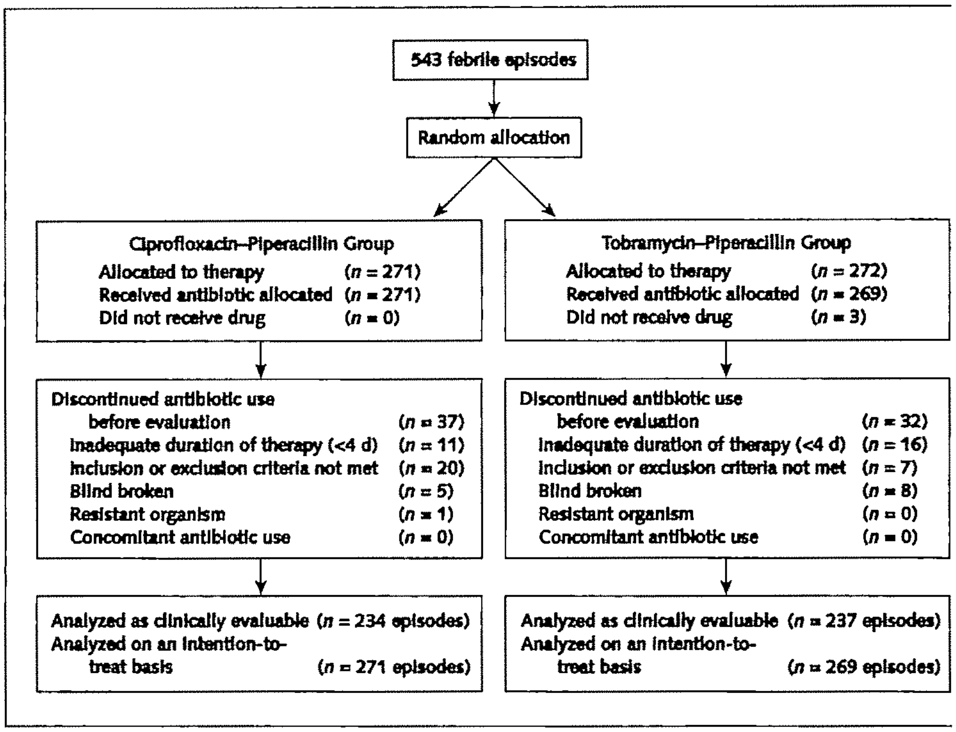
A total of 471 episodes met the criteria for clinical evaluability. Thirty-seven episodes in the ciprofloxacin–piperacillin group and 32 in the tobramycin–piperacillin group were excluded (13.7% vs. 11.9%, respectively; difference, 1.8 percentage points [CI, −4.2 to 7.8 percentage points]) (**Figure 2**). The most frequent reasons for exclusion were inadequate duration of therapy (n = 27) (occurring when patients had questionable infection and antibiotic use was discontinued before day 4) and violation of inclusion criteria (or meeting exclusion criteria) (n = 27).

We observed 295 infections in the 234 clinically evaluable episodes in the ciprofloxacin–piperacillin group and 311 infections in the 237 episodes in the tobramycin–piperacillin group. Clinically documented infections accounted for 43% of infections in each group. Microbiologically documented infection accounted for 29.1% of infections in the ciprofloxacin–piperacillin group and 35.7% in the tobramycin–piperacillin group. The two treatment groups did not differ significantly (P = 0.09) in the percentage of documented infections (65.4% in the ciprofloxacin–piperacillin group vs. 73.0% in the tobramycin–piperacillin group; difference, −7.6 percentage points [CI, −16.3 to 1.1 percentage points]). At least one organism was isolated from a baseline culture in 172 febrile episodes (36.6%) (78 in the ciprofloxacin–piperacillin group and 94 in the tobramycin–piperacillin group).

The most common infection, stomatitis, accounted for 26% to 30% of infections (**Table 2**). Pneumonia and urinary tract infections each occurred in 5% to 7% of patients. The treatment groups did not differ significantly in the sites of infections (P = 0.14). Bacteremias occurred in 15.6% of infections in the ciprofloxacin–piperacillin group and in 19.3% of infections in the tobramycin–piperacillin group (difference, −3.7 percentage points [CI, −13.6 to 2.3 percentage points]).

We noted 53 blood isolates in 48 patients in the ciprofloxacin–piperacillin group and 71 isolates in 61 patients in the tobramycin–piperacillin group. Among the types of blood isolates found, gram-positive isolates predominated, with 31 in the ciprofloxacin–piperacillin group and 38 in the tobramycin–piperacillin group. The most frequently seen gram-positive isolates were streptococcal species (34 isolates) followed by coagulase-negative staphylococci (24 isolates). The treatment groups did not differ significantly in the proportion of patients who had organisms isolated (33% of the ciprofloxacin–piperacillin group and 40% of the tobramycin–piperacillin group; difference, −7 percentage points [CI, −15.4% to 2.8%]) (P = 0.154). Forty-six gram-negative rods were isolated; among these, the most frequently found organisms were *Escherichia coli* and *Klebsiella* species. *Pseudomonas aeruginosa* was isolated from

Figure 2. Trial profile.


543 febrile episodes
Random allocation
Ciprofloxacin–Piperacillin Group
Allocated to therapy (n = 271)
Received antibiotic allocated (n = 271)
Did not receive drug (n = 0)
Tobramycin–Piperacillin Group
Allocated to therapy (n = 272)
Received antibiotic allocated (n = 269)
Did not receive drug (n = 3)
Discontinued antibiotic use before evaluation (n = 37)
Inadequate duration of therapy (<4 d) (n = 11)
Inclusion or exclusion criteria not met (n = 20)
Blind broken (n = 5)
Resistant organism (n = 1)
Concomitant antibiotic use (n = 0)
Discontinued antibiotic use before evaluation (n = 32)
Inadequate duration of therapy (<4 d) (n = 16)
Inclusion or exclusion criteria not met (n = 7)
Blind broken (n = 8)
Resistant organism (n = 0)
Concomitant antibiotic use (n = 0)
Analyzed as clinically evaluable (n = 234 episodes)
Analyzed on an intention-to-treat basis (n = 271 episodes)
Analyzed as clinically evaluable (n = 237 episodes)
Analyzed on an intention-to-treat basis (n = 269 episodes)

three patients receiving ciprofloxacin–piperacillin and from one patient receiving tobramycin–piperacillin.

We observed resistance to ciprofloxacin in 9.4% of baseline isolates, to tobramycin in 2%, and to piperacillin in 14.7%. Coagulase-negative staphylococcus constituted most of the resistant isolates. No aerobic gram-negative bacilli were resistant to ciprofloxacin, while only 1 *K. pneumoniae* isolate was resistant to tobramycin.

Efficacy

Table 3 shows the efficacy of the two therapies studied. Overall, episodes were treated successfully in 27% (63 of 234) of the clinically evaluable episodes in patients receiving ciprofloxacin–piperacillin compared with 22% (52 of 237) of the clinically evaluable episodes in patients receiving tobramycin–piperacillin (difference, 5.0 percentage points [CI, −2.3 to 12.8 percentage points]). No statisti-

Table 2. Major Sites of Infection

Site and Type of Infection	Ciprofloxacin–Piperacillin Group (234 Episodes)	Tobramycin–Piperacillin Group (237 Episodes)
	n (%)	
Bloodstream	48 (20.5)	61 (25.7)
Bacterial	46	60
Fungal	2	1
Gastrointestinal tract	102 (43.6)	102 (43)
Stomatitis	71	63
Enterocolitis	15	19
Perirectal cellulitis	8	12
Esophagitis	3	3
Pharyngitis	4	3
Periodontitis	1	2
Respiratory tract	21 (9)	28 (11.8)
Pneumonia	12	17
Sinusitis	9	11
Urinary tract (unspecified, upper or lower)	13 (5.5)	17 (7.2)
Integument	30 (12.8)	44 (18.6)
Cellulitis	6	10
Folliculitis	2	2
Venous access site	11	16
Tunnel	5	6
Exit site	6	10

Table 3. **Treatment of Infection: Efficacy***

Variable	Successfully Treated Infections		Differences (95% CI)
	Ciprofloxacin–Piperacillin Group	Tobramycin–Piperacillin Group	
	n/n (%)		*percentage points*
Total patients	63/234 (26.9)	52/237 (21.9)	5.0 (−2.3 to 12.8)
Patients with acute leukemia or bone marrow transplantation			0.4 (−7.4 to 9.2)†
CSF (stratum I)	14/70 (20)	15/68 (22.1)	
No CSF (stratum II)	15/96 (15.6)	12/90 (13.3)	
Patients with solid tumor or lymphoma			18.4 (1.8 to 31.7)‡
CSF (stratum III)	17/33 (51.5)	12/39 (30.8)	
No CSF (stratum IV)	17/35 (48.6)	13/40 (32.5)	

* Shown are data for the patients deemed clinically evaluable. CSF = received growth colony-stimulating factor; no CSF = did not receive growth colony-stimulating factor.
† The CI is for the difference in proportions between the ciprofloxacin–piperacillin group and the tobramycin–piperacillin group in patients with acute leukemia or a bone marrow transplant who had successfully treated infections.
‡ The CI is for the difference in proportions between the ciprofloxacin–piperacillin group and the tobramycin–piperacillin group in patients with a solid tumor or lymphoma who had successfully treated infections.

cally significant difference was noted among the strata regarding successful outcome of therapy ($P > 0.2$). In the patients with acute leukemia or a bone marrow transplant (strata I and II), the responses to ciprofloxacin–piperacillin versus tobramycin–piperacillin were similar (17.5% vs. 17.1%, respectively; difference, 0.4 percentage points [CI, −7.4 to 9.2 percentage points]). Patients with solid tumors or lymphomas (strata III and IV) who received ciprofloxacin–piperacillin had a higher rate of success than did patients who received tobramycin–piperacillin (50% [34 of 68] vs. 31.6% [25 of 79]; difference, 18.4 percentage points [CI, 1.8 to 31.7 percentage points]). We found similar results in the intention-to-treat patients; 26.6% of patients (72 of 271) receiving ciprofloxacin–piperacillin met the criteria for treatment success compared with 22.7% of patients (61 of 269) receiving tobramycin–piperacillin (difference, 3.9 percentage points [CI, −3.1 to 11 percentage points]).

All bacteremias except one were eradicated. The single episode of unresolved bacteremia involved a strain of group B streptococcus in a patient receiving tobramycin–piperacillin. The outcome of bacteremia was unknown in the 7% of episodes for which no follow-up cultures were obtained.

Outcome of therapy for documented infections was similar in each group: Treatment was successful for 22% of infections (33 of 153) in the ciprofloxacin–piperacillin group versus for 16% (27 of 173) in the tobramycin–piperacillin group (difference, 6 percentage points [CI, −0.8 to 15.2 percentage points]). Treatment response for fevers of unknown origin was similar in both groups (37% [30 of 81] in the ciprofloxacin–piperacillin group vs. 39% [25 of 64] in the tobramycin–piperacillin group responded; difference, −2 percentage points [CI, −19.3 to 15.3 percentage points]).

The most common reason for failure in both groups was modification of the antibiotic regimen. Antibiotic therapy was modified during the study period in 158 of 234 episodes in the ciprofloxacin–piperacillin group and in 171 of 237 episodes in the tobramycin–piperacillin group (67.5% vs. 72.2%; difference, −4.7 percentage points [CI, −13.3 to 4.1 percentage points]). Amphotericin B was the most commonly added agent in both groups, accounting for 28% of antibiotic additions in the ciprofloxacin–piperacillin group and 27% of additions in the tobramycin–piperacillin group. In 96.1% of these cases, amphotericin was added empirically for continued fever. Vancomycin was used empirically 62.5% of the time and was the agent added earliest in the course of therapy (median day of addition, 3). Vancomycin was the second most frequently added drug, followed by acyclovir and then fluconazole.

Figure 3 uses a Kaplan–Meier curve to show time to fever response in the clinically evaluable patients. Time to fever response was defined as the time from onset of fever until the first of 4 consecutive days with a sustained body temperature lower than 37.8 °C. Fever in the ciprofloxacin–piperacillin group resolved sooner than in the tobramycin–piperacillin group. The median time to fever response was 5 days in the ciprofloxacin–piperacillin group compared with 6 days in the tobramycin–piperacillin group ($P = 0.0052$). Seventeen percent of patients in the ciprofloxacin–piperacillin group compared with 30% of patients in the tobramycin–piperacillin group continued to have a fever during the study (difference, −13 percentage points [CI, −21.3 to −5.3 percentage points]).

The treatment groups did not differ in the secondary outcome variables. For survival during the neutropenic period, 96.2% of the clinically evaluable patients receiving ciprofloxacin–piperacillin survived compared with 94.1% of those receiving tobramycin–piperacillin (difference, 2.1 percentage points [CI, −2.2 to 6.4 percentage points]). Five patients in the tobramycin–piperacillin group were lost to follow-up before neutropenia resolved. Results were similar in the intention-to-treat patients; 94.5% of patients receiving ciprofloxacin–piperacillin survived versus 92.6% of those receiving tobramycin–piperacillin.

We observed no difference between groups in the incidence of subsequent infection or superinfection. Seventy-five patients receiving ciprofloxacin–piperacillin compared with 79 patients receiving tobramycin–piperacillin experienced either type of infection (32.1% vs. 33.3%; difference, −1.2 percentage points [CI, −10.2 to 7.6 percentage points]). Seven patients (2.99%) receiving ciprofloxacin–piperacillin and 13 patients (5.4%) receiving tobramycin–piperacillin had subsequent bacteremias. In the tobramycin–piperacillin group, 15 organisms were found, including 6 coagulase-negative staphylococci isolates; 3 *K. pneumoniae* isolates; and 1 isolate each of *E. coli*, *Proteus mirabilis*, *Streptococcus mitis*, *Bacteroides fragilis*, diphtheroids, and *Candida albicans*. In the ciprofloxacin–piperacillin group, 9 organisms were isolated, including 3 *S. aureus* isolates and 1 isolate each of coagulase-negative staphylococci, *B. uniformis*, *S. mitis*, *Hansenula anomala*, *C. parapsilosis*, and *C. lusitaniae*. Enterocolitis developed in 17 patients—9 in the ciprofloxacin–piperacillin group and 8 in the tobramycin–piperacillin group. Three patients (1.3%) receiving ciprofloxacin–piperacillin and four patients (1.7%) receiving tobramycin–piperacillin had a superinfection. In the ciprofloxacin–piperacillin group, all three superinfections involved bacteremia or fungemia. The organisms isolated were *C. parapsilosis*, *S. aureus*, and *B. uniformis*. In the tobramycin–piperacillin group, three patients developed bacteremia or fungemia (*S. mitis*, coagulase-negative staphylococci, and *C. albicans*), and one patient developed a streptococcal urinary tract infection. One patient receiving tobramycin–piperacillin had relapse of an *Enterobacter cloacae* infection of the urinary tract at 15 days after the end of therapy.

Safety

Adverse events, regardless of whether they appeared to be related to use of the study medication, were carefully recorded throughout the study (Table 4). Two hundred thirteen of the episodes in the ciprofloxacin–piperacillin group compared with 227 of the episodes in the tobramycin–piperacillin group (79% vs. 84%; difference, −5 percentage points [CI, −12.7 to 1.1 percentage points]) were associated with at least one adverse event that was categorized by the investigator as possibly or probably drug related. The most common side effects were hypokalemia, diarrhea, rash, abnormal renal function, and abnormal liver function tests, each of which was reported in approximately 20% to 30% of patients in each group. The treatment groups did not differ substantially in the nature or frequency of adverse events. Forty-five patients in the ciprofloxacin–piperacillin group and 49 patients in the tobramycin–piperacillin group stopped receiving the study medication because of an adverse event (17% vs. 18%; difference, −1 percentage point [CI, −8.4 to 5.2 percentage points]). In both groups, medication use was discontinued most often because of rash (in 52 patients) or abnormal kidney function (20 patients) or liver function (13 patients).

One hundred sixty-one patients in the study (29.8%) had elevations of at least 35 μmol/L (≥0.4 mg/dL) in serum creatinine level, which defined renal toxicity. The difference in elevations of serum creatinine levels between treatment groups was not significant (29.5% [80 patients] in the ciprofloxacin–piperacillin group vs. 30% [81 patients] in the tobramycin–piperacillin group; difference, −0.5 percentage points [CI, −8.7 to 7.5 percentage points]) ($P > 0.2$). When patients receiving other potential nephrotoxins were eliminated from our analysis, only 31 patients were identified as having probable antibiotic-related nephrotoxicity: 10 in the ciprofloxacin–piperacillin

Figure 3. **Kaplan–Meier curve showing time to fever response (product limit estimate) in patients valid for efficacy in the ciprofloxacin–piperacillin group (*solid line*) or tobramycin–piperacillin group (*dotted line*).**

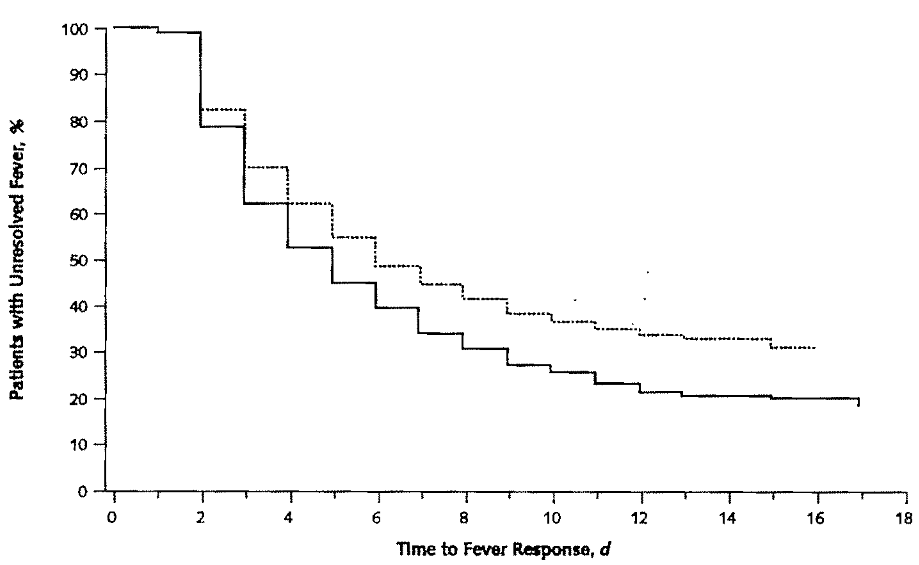


Table 4. **Adverse Events***

Type of Event†	Ciprofloxacin–Piperacillin Group (n = 271)	Tobramycin–Piperacillin Group (n = 269)	P Value
	n (%)		
Any event	213 (79)	227 (84)	0.083
Hypokalemia	76 (28)	71 (26)	>0.2
Rash	72 (27)	71 (26)	>0.2
Diarrhea	66 (24)	77 (29)	>0.2
Elevated ALT, AST, or alkaline phosphatase level	50 (18)	61 (23)	>0.2
Kidney function abnormalities	57 (21)	62 (23)	>0.2
Nausea	35 (13)	34 (13)	>0.2
Hyperglycemia	21 (8)	29 (11)	>0.2
Abdominal pain	22 (8)	23 (9)	>0.2
Vomiting	32 (12)	28 (10)	>0.2
Epistaxis	12 (4)	18 (7)	>0.2
Headache	16 (6)	16 (6)	>0.2
Hyperbilirubinemia	15 (6)	22 (8)	>0.2
Increased lactic dehydrogenase	14 (5)	21 (8)	>0.2
Pruritus	13 (5)	17 (6)	>0.2

* Events in the intention-to-treat population. The table shows events that were noted in at least 5% of the population. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

† Events judged by the investigator to possibly or probably be related to therapy.

group and 21 in the tobramycin–piperacillin group. Therefore, probable antibiotic-related nephrotoxicity occurred in 10 of 271 patients (3.6%) receiving ciprofloxacin–piperacillin versus in 21 of 269 patients (7.8%) receiving tobramycin–piperacillin (CI, −8.4% to −0.1%). Ninety-eight patients (18%) underwent baseline and posttherapy audiography. One patient in each group demonstrated decreased auditory acuity in one or both ears.

The treatment groups did not differ significantly in the number of patients who died during the study period or up to 30 days after administration of the final dose of the study medication. Eighteen patients who received ciprofloxacin–piperacillin died compared with 23 patients who received tobramycin–piperacillin (6.6% vs. 8.5%, respectively; difference, −1.9 percentage points [CI, −6.7 to 2.9 percentage points]) ($P > 0.2$). The cause of death was comorbid illness in 68% of cases. One patient in the ciprofloxacin–piperacillin group and 2 patients in the tobramycin–piperacillin group died of the initial bacterial infection. Subsequent bacterial infection was identified as the cause of death in one patient in the ciprofloxacin–piperacillin group and in three patients in the tobramycin–piperacillin group. The cause of death was unknown in five patients.

DISCUSSION

Aminoglycoside plus antipseudomonas β-lactam combinations have represented traditional treatment for neutropenic fever since the 1970s, when Schimpff and colleagues (1) first demonstrated their efficacy. The major drawback to aminoglycoside use has been the possibility of nephrotoxicity and ototoxicity. Wide ranges of toxicity have been reported, with commonly acknowledged rates of 5% to 14% for nephrotoxicity and up to 41% for ototoxicity (23–26). The risk for nephrotoxicity may be further increased by concurrent administration of other potential nephrotoxins, including amphotericin B, cyclosporine, diuretics, or cisplatin.

Although monotherapy has been used in this patient population with third-generation cephalosporins (for example, cefepime or ceftazidime) and carbapenems (for example, meropenem or imipenem), combination therapy remains an important therapeutic option, in part because of development of resistance to these agents and toxicity. Ciprofloxacin is an attractive potential alternative in patients with febrile neutropenia because of its activity against aerobic gram-negative bacilli, including *P. aeruginosa*, and its potential synergy with β-lactam compounds (8–10, 27). When used as monotherapy, response rates similar to those seen in controls, at 60% to 88%, have been reported (12, 13, 19, 22). However, small numbers of patients, a marked variety of underlying diseases, varying degrees and duration of neutropenia, and various dosing schedules have made interpretation of the data difficult. A single study demonstrated that relatively low dosing of ciprofloxacin, at 200 to 300 mg intravenously every 12 hours, led to suboptimal responses (14). This finding, the importance of gram-positive cocci, and the concern of resistance led to the successful use of high-dose ciprofloxacin, at 400 mg intravenously every 8 hours (28).

Studies of combination therapy using ciprofloxacin have reported mostly favorable outcomes (18, 19). In a study similar to ours, Griggs and colleagues (18) compared ciprofloxacin plus piperacillin with gentamicin plus piperacillin. Although only 96 patients were randomly allocated, most were recipients of bone marrow transplantation with long-standing neutropenia. Overall, success rates in patients receiving ciprofloxacin were similar to those observed in controls. The ciprofloxacin-containing regimen provided significantly faster resolution of fever in patients with fevers of unknown origin and with gram-negative bacteremia. As was typical in earlier studies, other antimicrobial agents, usually vancomycin or amphotericin, were added to the regimen in 56% to 70% of patients in both study groups. Most recently, oral ciprofloxacin has been used successfully as part of combination therapy in patients with neutropenia expected to be of short duration with no associated complicating conditions (29–31).

Several important features of our study design are noteworthy. First, to our knowledge, this study represents the largest controlled trial of ciprofloxacin in neutropenic patients. Furthermore, patients were stratified according to the nature of the underlying disease and the use of colony-stimulating factors. This assured comparison of groups with a similar degree and duration of neutropenia. A strict definition of antibiotic success was used so that the addition of any antimicrobial agent to the initial regimen would be viewed as a failure whether the addition was an antibacterial, antiviral, or antifungal agent. The goal was to unambiguously define the adequacy of each regimen to treat neutropenic fever. This resulted in a relatively low response rate in both groups when compared with the rates reported in other recent studies; however, the response rate in our study was similar to that of other studies that have used similar strict definitions (32–34).

In our study, although the overall efficacy of ciprofloxacin–piperacillin was similar to that of tobramycin–piperacillin, the ciprofloxacin–piperacillin regimen produced a higher success rate in patients with lymphoma and solid tumors than did the regimen involving tobramycin. Use of ciprofloxacin led to normalization of fever 1 day earlier than did tobramycin—a finding also observed previously by Griggs and colleagues (18). Persons taking regimens with a more rapid time to response have been shown to have shorter hospital stays and lower costs of care (35). Although neither length of stay nor cost of care were measured in this study, our finding of shorter fever duration may significantly affect quality and cost of care if it can be substantiated.

The incidence of toxicity was similar in both treatment groups. Previous studies have also reported similar rates of nephrotoxicity for both regimens (18). The use of other potential nephrotoxins complicates the evaluation of renal toxicity related to use of the study medication. However, when we eliminated patients receiving other potential nephrotoxins from our analysis, probable tobramycin-related toxicities were more common than probable ciprofloxacin-related nephrotoxicity. Ototoxicity was similarly difficult to evaluate. Because of severity of illness, only 98 study patients (18%) underwent repeated audiography.

Caution is warranted because of increased ciprofloxacin resistance at many centers. Resistance rates in gram-negative bacilli as high as 24% have been observed, representing a major change since the completion of this study, when no resistant gram-negative bacilli had been noted (36, 37). Researchers have observed similar increases in the rate of resistance to most antibiotics that are commonly used alone or in combination in patients with febrile neutropenia (36, 38). Because resistance patterns vary greatly by geography (39) and clinical setting (40), susceptibility patterns need to be reviewed regularly to determine the usefulness of any antibiotic, independent of reports in the literature.

To our knowledge, this study is the first large, controlled, double-blind examination of ciprofloxacin as part of a combination regimen for empirical therapy of neutropenic fever. Our results clearly establish that use of ciprofloxacin, at a dose of 400 mg administered intravenously every 8 hours, in combination with piperacillin is at least as effective as use of tobramycin plus piperacillin as empirical therapy of fever in patients with neutropenia. This study adds another clinically proven regimen to the therapeutic options available for this most-difficult-to-treat patient population.

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ARTICLE

Use of the Electrocardiograph-Based Thrombolytic Predictive Instrument To Assist Thrombolytic and Reperfusion Therapy for Acute Myocardial Infarction

A Multicenter, Randomized, Controlled, Clinical Effectiveness Trial

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Background: Deciding which patients should receive thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI) can be difficult, especially for less-obvious candidates and when consulting physicians are off site.

Objective: To test whether the electrocardiograph-based Thrombolytic Predictive Instrument (TPI) improves use of thrombolytic and overall reperfusion therapy.

Design: 22-month randomized, controlled, clinical effectiveness trial.

Setting: Emergency departments at 28 urban, suburban, and rural hospitals in the United States.

Patients: Persons presenting to the emergency department with AMI and ST-segment elevation on an electrocardiogram (ECG).

Intervention: TPI predictions automatically printed on ECG text headers.

Measurements: Percentages of patients receiving thrombolytic therapy, thrombolytic therapy within 1 hour of initial ECG, and overall reperfusion (thrombolytic therapy or PTCA).

Results: Of 2875 patients with AMI, 1243 (43.2%) had ST-segment elevation. Of these, 1197 were randomly assigned to study groups; 732 (61.2%) had inferior AMI, and 465 (38.8%) had anterior AMI. A total of 60.5% of controls and 62.1% of TPI patients ($P = 0.2$) received thrombolytic therapy, 52.5% of controls and 53.3% of TPI patients received thrombolytic therapy within 1 hour ($P > 0.2$), and 67.6% of controls and 70.3% of TPI patients received overall reperfusion ($P = 0.2$). Of patients with inferior AMI in the control group versus the TPI group, 61.1% versus 67.6% ($P = 0.03$) received thrombolytic therapy, 53.2% versus 58.6% ($P = 0.08$) received thrombolytic therapy within 1 hour, and 67.7% versus 74.7% ($P = 0.03$) received overall reperfusion. Of patients with anterior AMI in the control group versus the TPI group, 59.5% versus 53.9% ($P > 0.2$) received thrombolytic therapy, 51.4% versus 45.3% ($P > 0.2$) received thrombolytic therapy within 1 hour, and 67.6% versus 63.8% ($P > 0.2$) received overall reperfusion. Among women ($n = 398$) in the control group versus the TPI group, 48.1% versus 58.2% ($P = 0.03$) received thrombolytic therapy, 40.5% versus 48.4% ($P = 0.10$) received thrombolytic therapy within 1 hour, and 55.7% versus 65.7% ($P = 0.04$) received overall reperfusion. Of patients who required physician consultation by telephone ($n = 271$) in the control group versus the TPI group, 47.3% versus 63.2% ($P = 0.01$) received thrombolytic therapy, 41.1% versus 53.6% ($P = 0.04$) received thrombolytic therapy within 1 hour, and 50.7% versus 66.4% ($P = 0.01$) received overall reperfusion.

Conclusions: The TPI increased use of thrombolytic therapy, use of thrombolytic therapy within 1 hour, and use of overall coronary reperfusion by 11% to 12% for patients with inferior AMI, 18% to 22% for women, and 30% to 34% for patients with an off-site physician. Although its effect was minimal on patients with high baseline reperfusion rates, the TPI increased use and timeliness of reperfusion in often-missed groups and when involved physicians were off site.

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Emergent coronary reperfusion for acute myocardial infarction (AMI) can be lifesaving for appropriate patients who are promptly recognized and treated (1–4). However, in the emergency department setting, this prompt recognition can be difficult, especially for less-obvious candidates and when physician decision makers are not all on site. To assist in treatment decisions, the Thrombolytic Predictive Instrument (TPI), incorporated into conventional computerized electrocardiography, prints on the electrocardiogram (ECG) text header its predictions of key outcomes of thrombolytic therapy: 30-day mortality, 1-year mortality, cardiac arrest, hemorrhagic stroke, and bleeding requiring transfusion (5, 6).

Over the past decade, as a result of intensive efforts by physician leaders, the U.S. National Institutes of Health National Heart Attack Alert Program, organizations interested in quality of medical care, the pharmaceutical industry, and others (3, 7–16), more patients with AMI have received thrombolytic therapy and have received it sooner (17). However, further improvement is needed (17–20), especially for patients with AMI other than anterior AMI (the category of AMI for which thrombolytic therapy was first recognized as effective [1, 2]) and for women (who have received reperfusion therapy at lower rates than men [18, 20]). Also needed are ways to support prompt, accurate decisions about reperfusion therapy in hospitals and in prehospital emergency medical service (EMS) settings where consultation with off-site physicians may be required. The need for prompt recognition of potential benefit also applies to acute reperfusion by primary percutaneous transluminal coronary angioplasty (PTCA), which may be equivalent to thrombolytic therapy or even preferable

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Context

Decision making about thrombolysis in acute myocardial infarction (AMI) can be difficult. The Thrombolytic Predictive Instrument (TPI) estimates the risk for death and hemorrhage with and without thrombolysis. Its effect on patient care is unknown.

Contribution

This randomized trial of the TPI in emergency departments showed that printing TPI predictions on the admission electrocardiogram increased the frequency of reperfusion for inferior AMI but not anterior AMI. The effect of the TPI was greatest for women and for patients who required off-site consultation.

Implications

The TPI is a tool to assure all patients the same standard of care.

–The Editors

for some patients with AMI (21–25). Thus, any method of increasing use of thrombolytic therapy should not interfere with the alternative use of PTCA, when indicated.

To test whether the TPI addresses these needs, we did a randomized, controlled, clinical effectiveness trial in the emergency departments of 28 diverse hospitals. We sought to determine whether the TPI would help physicians 1) identify patients needing thrombolytic therapy who would not otherwise have been identified; 2) use thrombolytic therapy sooner; 3) identify more candidates for overall coronary reperfusion, including medical thrombolysis or primary PTCA; and 4) expedite decisions about reperfusion when physician decision makers are not all on site.

METHODS

Study Sites

Our study was done in 28 U.S. hospitals, including public, private, community, and tertiary care hospitals in urban, suburban, and rural areas: Bess Kaiser Medical Center (Portland, Oregon), Boston City Hospital (Boston, Massachusetts), Box Butte General Hospital (Alliance, Nebraska), Carney Hospital (Dorchester, Massachusetts), Cedars-Sinai Medical Center (Los Angeles, California), Chadron Community Hospital (Chadron, Nebraska), Cooley Dickinson Hospital (Northampton, Massachusetts), Decatur County Hospital (Oberlin, Kansas), Franklin Medical Center (Greenfield, Massachusetts), Huntington Hospital (Huntington, New York), Lincoln Community Hospital (Hugo, Colorado), Mary Lane Hospital (Ware, Massachusetts), Memorial Health Center (Sidney, Nebraska), Memorial Hospital (Craig, Colorado), New England Medical Center (Boston, Massachusetts), Noble Hospital (Westfield, Massachusetts), North Shore University Hospital–Glen Cove (Glen Cove, New York), Plains Medical Center (Limon, Colorado), Presbyterian/St. Luke's Medical Center (Denver, Colorado), Regional West Medical Center (Scottsbluff, Nebraska), Rhode Island Hospital (Providence, Rhode Island), Silverheels Health Center (Fairplay, Colorado), Southeast Colorado Hospital (Springfield, Colorado), Sunnyside Medical Center (Clackamas, Oregon), Swedish Hospital (Engelwood, Colorado), Timberline Medical Center (Granby, Colorado), University Hospital (Boston, Massachusetts), and University Hospital–Stony Brook (Stony Brook, New York).

Patients and Intervention

We included all consenting patients 35 years of age and older who 1) presented with AMI to any study hospital during the 22-month period beginning 24 April 1995 and 2) had, on presentation to the emergency department, detection of ST-segment elevation characteristic of AMI on an ECG.

At study hospitals, software that generated the TPI predictions was installed on conventional computerized electrocardiographs (Hewlett-Packard, Palo Alto, California) so that ST-segment elevation characteristic of AMI was automatically detected. When this elevation was detected, the patient was automatically randomly assigned to the control or the TPI group. Randomization did not delay obtaining an ECG or treatment. (In accordance with Institutional Review Board approval [given that usual ECGs and ECGs with TPI predictions both represent standard care and that it is necessary not to disrupt initial emergency care], we obtained written informed consent as soon as was practical after the initial ECG.) For patients in the TPI group, the electrocardiograph automatically prompted the user to enter patient information needed to make the TPI predictions: age, sex, history of hypertension, history of diabetes, blood pressure, and time since onset of ischemic symptoms. The remaining variables, based on measurement of ECG waveforms, were automatically acquired by the electrocardiograph. Then the ECG was printed with the TPI predictions on its header. If any variables for the calculations were missing, predictions were not calculated and an alert listing the missing variables was printed. Entry of missing data, if available, was allowed. Predictions were not generated for patients older than 75 years of age (5, 26, 27). For controls, the ECG was automatically printed with the header text customarily used in that emergency department.

Data Collection and Analysis

At presentation and during hospitalization, we collected sociodemographic information; data on clinical features, ECGs, and all cardiac biomarker test results (at minimum, serial creatine kinase MB tests) at presentation and follow-up; the triaging physician's training level and specialty and whether he or she was emergency department–based; whether on- or off-site (telephone) consultations were used in making the reperfusion treatment decision; whether the patient received thrombolytic therapy and, if so, the time from onset of chest pain to receipt of therapy; and whether the patient received primary PTCA. The TPI software allowed real-time acquisition of the clinical variables required for the TPI calculations and automatic acquisition of Q-wave, ST-segment, and T-wave measurements. Follow-up data needed to assign confirmed "true" diagnoses were collected from arrival at the emergency department through the 30-day follow-up visit. The overall 30-day follow-up rate was 100%.

Site physicians, blinded to study group assignments, used World Health Organization criteria (28) to assign confirmed diagnoses on the basis of presentation, clinical course, initial and follow-up ECGs, and biomarker tests. An AMI was classified as anterior if the patient had at least two contiguous ECG anterior leads with ST-segment elevation, regardless of whether this was accompanied by elevation elsewhere. Any AMI with no significant anterior ST-segment elevation was classified as inferior. Emergency department care was classified by whether consultation with an off-site physician was used in making the treatment decision. Hospital size, hospital type, presence of on-site emergency department staff, and physician type were used as potentially explanatory variables.

Statistical Analysis

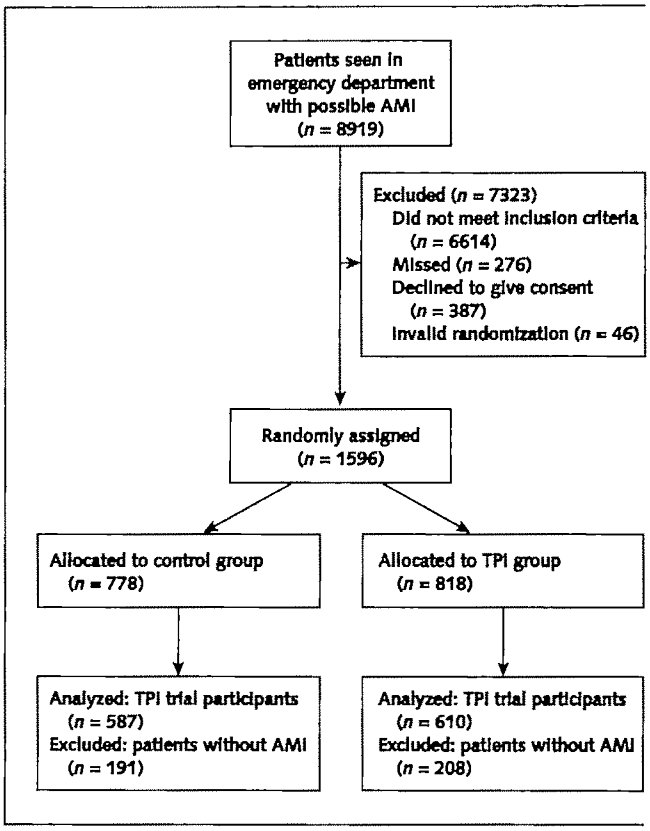
Baseline comparisons of patient characteristics between the control and TPI groups were done by using *t*-tests for continuous variables and chi-square tests for categorical variables. Because of skewed distributions of times from symptom onset, median times from symptom onset to initial ECG were compared between groups by using the Wilcoxon rank-sum test. Chi-square tests for 2 × 2 tables were used to compare crude differences between groups in rates of use of thrombolytic therapy; use of thrombolytic therapy within 1 hour of randomization; and overall use of reperfusion, including PTCA. The predictive discrimination of the TPI's mortality predictions was measured by using the area under the receiver-operating characteristic (ROC) curve, estimated by the *c* statistic from the logistic regression model predicting the outcome with the predicted values as the sole independent variable.

Relative risks and *P* values were derived from the 2 × 2 tables and chi-square tests. Analyses by AMI location and patient sex were also adjusted for hospital type (urban teaching hospital, teaching-affiliated hospital, or community or rural hospital) by using the Cochran–Mantel–Haenszel test. Hospital groupings were made before analyses were done and reflect similar characteristics and expected reperfusion rates. Commonality of the relative risk across hospital type was tested by using the Breslow–Day chi-square statistic. We used SAS, version 8 (SAS, Inc., Cary, North Carolina) for all analyses.

Role of the Funding Source

Neither the funding source nor the manufacturers of equipment or software had any role in the collection, analysis, or interpretation of data or in the writing or submission of this paper for publication. Primary data analyses, including breaking of the randomization code, were done first by an outside independent statistician on the Data Monitoring and Safety Committee.

Figure. **Patient Inclusion.**


Patients seen in emergency department with possible AMI (n = 8919)
Excluded (n = 7323)
Did not meet inclusion criteria (n = 6614)
Missed (n = 276)
Declined to give consent (n = 387)
Invalid randomization (n = 46)
Randomly assigned (n = 1596)
Allocated to control group (n = 778)
Allocated to TPI group (n = 818)
Analyzed: TPI trial participants (n = 587)
Excluded: patients without AMI (n = 191)
Analyzed: TPI trial participants (n = 610)
Excluded: patients without AMI (n = 208)

AMI = acute myocardial infarction; TPI = Thrombolytic Predictive Instrument.

RESULTS

As shown in the **Figure**, a total of 8919 patients with possible AMI were screened for study eligibility. Of 3266 eligible patients with AMI, 2879 (88%) consented to participate; 1237 (43%) had AMI with ST-segment elevation detected and were randomly assigned to study groups by the electrocardiograph. Of these 1237 patients, 40 (3.2%) had two different randomization assignments and thus were excluded from the trial. Of the 1197 patients included in the trial, those assigned to the control group (n = 587) and those assigned to the TPI group (n = 610) were similar, except for trends toward more previous coronary artery disease in the control group and more diabetes in the TPI group (Table 1). The 1642 consenting patients with AMI without ST-segment elevation were included in a "non-trial" registry.

For safety, we monitored patients who had ST-segment elevation detected but did not have AMI. The control group had 191 such patients, of whom 1 (0.5%) received thrombolytic therapy; the TPI group had 208 such patients, of whom 3 (1.4%) received thrombolytic therapy

Table 1. **Presenting Characteristics of Patients with Acute Myocardial Infarction Who Were Randomly Assigned to Study Groups***

Characteristic	Control Group (*n* = 587)	TPI Group (*n* = 610)	*P* Value
Mean age, *y*	63.8	63.6	>0.2
Male sex, %	68.5	65.1	0.2
Ethnicity, %			
White	91.7	91.6	
Black	4.1	4.8	>0.2
Hispanic	2.7	2.0	
Other	1.5	1.6	
Mean systolic blood pressure	142.9	142.4	>0.2
Median time from onset of symptoms to arrival at the emergency department (25th, 75th percentile), *min*	142 (81, 279)	131 (79, 265)	>0.2
Clinical features, %			
History of hypertension	50.9	51.0	>0.2
History of coronary artery disease	37.8	34.1	0.18
History of diabetes	18.2	22.5	0.07
Previous MI	27.8	24.1	0.15
Anterior acute MI	37.8	39.8	>0.2
Previous thrombolytic therapy	5.7	6.8	>0.2
Previous stroke	5.6	4.1	>0.2

* MI = myocardial infarction; TPI = Thrombolytic Predictive Instrument.

($P > 0.2$). We also monitored use of thrombolytic therapy in patients with contraindications; the control group had two such patients (0.6%), and the TPI group had one (0.3%) ($P > 0.2$). The rate of use of thrombolytic therapy for study patients was 69.0%. Use varied by type of hospital, with observed rates of 46.3%, 73.5%, and 70.5% in urban teaching, teaching-affiliated, and rural or community hospitals, respectively. Across all hospitals, 52.9% of patients received thrombolytic therapy within 1 hour (39.8% at urban teaching hospitals, 65.0% at teaching-affiliated hospitals, and 59.0% at rural or community hospitals). The rate of overall reperfusion, including thrombolytic therapy or primary PTCA, was 62.8% at urban teaching hospitals, 74.3% at teaching-affiliated hospitals, and 72.5% at rural or community hospitals. Neither patient sex nor AMI location differed significantly by hospital type.

Table 2 shows that printing TPI predictions on the ECG significantly improved reperfusion rates for inferior, but not anterior, AMIs. Among the 732 patients (61.2%) with inferior AMI, 61.1% of those in the control group and 67.6% of those in the TPI group received thrombolytic therapy ($P = 0.03$); 53.2% of those in the control group and 58.6% of those in the TPI group received this therapy within 1 hour ($P = 0.08$). Rates of overall reperfusion (thrombolytic therapy or primary PTCA) were 67.7% in the control group and 74.7% in the TPI group ($P = 0.03$). These absolute changes of 5 to 7 percentage points represent relative changes of 11% to 12%. Among the 465 trial patients (38.8%) with anterior AMI, no significant differences were seen between the control and TPI groups, as shown by relative risks of 0.9 to 1.0 ($P > 0.2$) for each reperfusion treatment measure.

Table 3, in which patients with inferior and anterior AMIs are combined, shows the effect of the TPI in women and men. In women, TPI increased the rate of use of thrombolytic therapy from 48.1% to 58.2% ($P = 0.03$), increased the rate of use of thrombolytic therapy within 1 hour from 40.5% to 48.4% ($P = 0.10$), and increased the rate of use of overall reperfusion from 55.7% to 65.7% ($P = 0.04$). These absolute increases of 8 to 10 percentage points represent relative increases of 18% to 22%. In men, when those with inferior and those with anterior AMIs were combined, the effect of TPI was not significant.

Table 4 shows the effect of the TPI when telephone consultation with an off-site primary care physician or cardiologist was required. When consultation was done entirely by telephone ($n = 271$), 47.3% of the control group and 63.2% of the TPI group received thrombolytic therapy ($P = 0.01$), 41.1% of the control group and 53.6% of the TPI group received thrombolytic therapy within 1 hour ($P = 0.04$), and 50.7% of the control group and 66.4% of the TPI group received overall reperfusion ($P = 0.01$). These absolute changes of 13 to 16 percentage points represent relative changes of 30% to 34%. Consistent effects were seen in separate subgroup analyses for telephone consultations with primary care physicians and cardiologists.

Table 5 shows the effect of TPI among the 56 patients

Table 2. **Effect of the Thrombolytic Predictive Instrument on Treatment of Patients with Acute Myocardial Infarction by Location of Infarction***

Patients	Treatment Received	Control Group (*n* = 587), %	TPI Group (*n* = 610), %	Relative Risk with TPI (95% CI)†	*P* Value†
All patients (*n* = 1197)	Thrombolytic therapy within 1 hour	52.5	53.3	1.0 (0.9–1.2)	>0.2
	Thrombolytic therapy	60.5	62.1	1.1 (0.96–1.1)	0.2
	Thrombolytic therapy or PTCA	67.6	70.3	1.0 (0.97–1.1)	0.2
Patients with inferior AMI (*n* = 732)	Thrombolytic therapy within 1 hour	53.2	58.6	1.1 (0.9–1.3)	0.08
	Thrombolytic therapy	61.1	67.6	1.1 (1.01–1.2)	0.03
	Thrombolytic therapy or PTCA	67.7	74.7	1.1 (1.01–1.2)	0.03
Patients with anterior AMI (*n* = 465)	Thrombolytic therapy within 1 hour	51.4	45.3	0.9 (0.8–1.1)	>0.2
	Thrombolytic therapy	59.5	53.9	0.9 (0.8–1.1)	>0.2
	Thrombolytic therapy or PTCA	67.6	63.8	1.0 (0.8–1.1)	>0.2

* AMI = acute myocardial infarction; PTCA = primary percutaneous transluminal coronary angioplasty; TPI = Thrombolytic Predictive Instrument.
† Adjusted for type of hospital.

Table 3. **Effect of the Thrombolytic Predictive Instrument on Treatment of Patients with Acute Myocardial Infarction by Patient Sex***

Patients	Treatment Received	Control Group (n = 587), %	TPI Group (n = 610), %	Relative Risk with TPI (95% CI)†	*P* Value†
Women (n = 398)	Thrombolytic therapy within 1 hour	40.5	48.4	1.2 (0.96–1.5)	0.10
	Thrombolytic therapy	48.1	58.2	1.2 (1.01–1.5)	0.03
	Thrombolytic therapy or PTCA	55.7	65.7	1.2 (1.0–1.4)	0.04
Men (n = 799)	Thrombolytic therapy within 1 hour	58.0	55.9	1.0 (0.9–1.1)	>0.2
	Thrombolytic therapy	66.2	64.2	1.0 (0.9–1.1)	>0.2
	Thrombolytic therapy or PTCA	73.1	72.8	1.0 (0.9–1.1)	>0.2

* PTCA = primary percutaneous transluminal coronary angioplasty; TPI = Thrombolytic Predictive Instrument.
† Adjusted for type of hospital.

seen at hospitals without on-site emergency department physicians. The small size of this group limits our ability to detect statistical significance, but the results show absolute increases of 18 to 26 percentage points in use of thrombolytic therapy, use of thrombolytic therapy within 1 hour, and overall reperfusion, representing relative increases of 44% to 53%. The TPI predictions of 30-day mortality were very good, as shown by the area under the ROC curve of 0.82 for all patients, 0.85 for recipients of thrombolytic therapy, and 0.84 for PTCA recipients. These models were also well calibrated, with similar agreement between observed and predicted mortality rates across the entire risk range.

Although this trial was not powered to detect significant differences in mortality and stroke rates, we monitored these outcomes for safety reasons. Overall mortality rates were 3.4% in the control group and 5.0% in the TPI group (P = 0.15). When these rates were corrected for the higher rate of diabetes in the TPI group, again, they did not differ significantly ($P > 0.2$). Three strokes each (0.5%) occurred in the control and TPI groups ($P > 0.2$). Thrombolysis-related bleeding requiring transfusion occurred in 16 controls (4.5%) and 22 patients in the TPI group (5.8%) ($P > 0.2$).

DISCUSSION

This multicenter, controlled, clinical effectiveness trial tested the effect of having an electrocardiograph automatically print, on the ECGs of patients presenting to emergency departments, TPI predictions of the benefit of thrombolytic therapy for AMI. Although the intervention had minimal effect in patient groups with already-high rates of reperfusion, it increased and expedited use of thrombolytic and overall reperfusion therapy for patients typically treated less often or less quickly. In patients with inferior AMI, the TPI significantly increased rates of use of thrombolytic therapy, use of thrombolytic therapy within 1 hour of arrival at the emergency department, and use of overall acute reperfusion (thrombolytic therapy or primary PTCA), all by 11% to 12% (**Table 2**). It seems that the TPI helped physicians recognize the need for reperfusion in patients with inferior AMIs; this is the most common location of AMI, although less typically targeted for reperfusion (29). For both inferior and anterior AMIs, we confirmed earlier findings (18, 20) that women receive reperfusion less often than men. This difference was corrected when the TPI was used. The lower baseline proportions of women receiving thrombolytic therapy, receiving thrombolytic therapy within 1 hour, and receiving any reperfusion increased by 18% to 22% (**Table 3**). This suggests that the TPI was particularly useful for patients whose need for reperfusion is currently less well recognized.

The TPI also increased use and promptness of reperfusion in situations with logistic impediments to treatment. Delays in use of thrombolytic therapy occur when consultation with an off-site physician is needed (20, 30); the TPI's effect was pronounced in this setting. Among all patients with AMI in this situation, the TPI increased rates of use of thrombolytic therapy, use of thrombolytic therapy within 1 hour, and use of overall acute reperfusion, all by 30% to 34% (**Table 4**). This was underscored by even larger increases (44% to 53%) among patients seen at hospitals without on-site emergency department physicians (**Table 5**). These results suggest that use of the TPI in emergency departments where off-site physician consultation is needed, and possibly in EMS settings where physician supervision is entirely remote, should increase the use and timeliness of reperfusion. Given the prevalence of these settings across the United States, this could have a substantial nationwide effect on the treatment of AMI.

Many programs have been developed to increase use of thrombolytic and reperfusion therapy for AMI (3, 7–16), but individual patient–specific approaches have not previously been used. Currently, to make a decision about reperfusion in practice, physicians must recall results from controlled clinical trials that apply to general classes of patients (for example, early vs. late presentation, anterior vs. inferior AMI, large vs. small AMI, and younger vs. older patients) obtained from medical journals, pharmaceutical representatives, colleagues, and guidelines. In contrast, the TPI gives the physician specific predictions of the effect of thrombolytic therapy based on a particular patient's presenting features; vital signs; time since symptom onset; and detailed ECG indices of AMI earliness (in relation to the infarction process), location, and size (5, 6, 31, 32). These predictions apply the results of the many clinical trials on which the TPI models are based to specific patients. These predictions, generated when the TPI pro-

Table 4. **Effect of the Thrombolytic Predictive Instrument on Patients with Acute Myocardial Infarction for Whom Physician Consultation Was Entirely by Telephone (n = 271)***

Treatment Received	Control Group (n = 146), %	TPI Group (n = 125), %	Relative Risk with TPI (95% CI)	P Value
Thrombolytic therapy within 1 hour	41.1	53.6	1.3 (1.01–1.7)	0.04
Thrombolytic therapy	47.3	63.2	1.3 (1.2–3.1)	0.01
Thrombolytic therapy or PTCA	50.7	66.4	1.3 (1.1–1.6)	0.01

* PTCA = primary percutaneous transluminal coronary angioplasty; TPI = Thrombolytic Predictive Instrument.

gram detects ST-segment elevation consistent with AMI, seem to supplement (but not replace) physicians' decision making about treatment for specific patients.

General and patient-specific approaches probably both work, and they may well supplement each other. Indeed, the relatively high rates of thrombolytic and overall reperfusion therapy for patients with AMI, about 43% in our study, confirm improvements as a result of ongoing general attempts to improve use of thrombolytic therapy. However, room for improvement may still exist, as shown by use rates greater than 50% in Europe (33) and the fact that some groups, particularly women (17, 18, 20, 33, 34) and patients with inferior AMI (35), still seem to be undertreated. The TPI's improved rates of reperfusion among women and patients with inferior AMI suggest that additional improvement results from real-time, patient-specific support for decision making. This support also seems to help when no emergency department physician is on site or when needed consultation is available only by telephone; both situations are associated with delays in reperfusion (20, 30), and these delays are lessened with TPI use. This effect is analogous to that of the patient-specific predictions of the electrocardiograph-based acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI), which most improves emergency department triage for patients cared for by unsupervised residents and patients with stable angina pectoris, for whom improved decision making is needed (36, 37). It seems that real-time bedside support for patient-specific decision making may build on and enhance the effect of general efforts to improve care for AMI.

It is hard to project the likely effect of the TPI on AMI-related mortality rates nationwide. Patients with small inferior AMIs have relatively low mortality rates, and increased reperfusion will therefore yield relatively small absolute benefits in survival in these patients (38). However, given that more than 60% of AMIs are inferior (34) and that the survival benefit of increased reperfusion for large inferior AMIs approaches that for anterior AMIs, the effect seen in our trial for inferior AMI should benefit many patients. In addition, improved survival rates for women, who are more likely to die of AMI, will have an important effect. Projected nationwide, the relative increases seen in our trial (10% for patients with inferior AMI and 20% for women with AMI) in rates of thrombolytic therapy, thrombolytic therapy within 1 hour, and overall reperfusion should be substantial. Additional effects can be expected from the TPI's effect on care when consultation with an off-site physician is needed or when a full-time emergency department physician is lacking; these situations are associated with longer times to reperfusion and potentially higher mortality rates (20, 30). Moreover, as prehospital thrombolytic treatment becomes more common for patients with long transport times to hospitals, the substantial effect of the TPI on rates of reperfusion in such settings, and thereby on rates of death from AMI, should increase.

It is noteworthy that when we pooled all trial settings, the TPI's effect was not seen among patients with anterior AMI and, when AMI locations were combined, among men. The need for reperfusion in patients with anterior AMIs has been emphasized longer than the need for reperfusion in patients with inferior AMIs, and anterior AMIs are more easily recognized in the precordial leads of the conventional ECG. Physicians are already skilled at identifying patients with anterior AMIs as candidates for reperfusion, and at treating them. In addition, AMI presents more "classically" and is better recognized (and treated) in men than women (39–41). The high rates of reperfusion for patients with anterior AMI and for men in experienced centers may require little improvement. However, although fewer than 5% of our patients were seen in hospitals without on-site emergency department physicians, and although none were treated while in transit to the hospital via EMS (when all physician input would be remote), our results show improvement in the speed and use of reperfu-

Table 5. **Effect of the Thrombolytic Predictive Instrument on Patients with Acute Myocardial Infarction Who Presented to Hospitals without an On-Site Emergency Department Physician (n = 56)***

Treatment Received	Control Group (n = 22), %	TPI Group (n = 34), %	Relative Risk with TPI (95% CI)	P Value
Thrombolytic therapy within 1 hour	40.9	58.8	1.4 (0.8–2.6)	0.19
Thrombolytic therapy	50.0	76.5	1.5 (0.97–2.4)	0.04
Thrombolytic therapy or PTCA	54.6	79.4	1.5 (0.96–2.2)	0.05

* PTCA = primary percutaneous transluminal coronary angioplasty; TPI = Thrombolytic Predictive Instrument.

sion among all patients with AMI (including men and those with anterior AMI) when the emergency department physician or needed physician consultants are off site. Given that many emergency departments are not staffed 24 hours per day and that, especially in rural settings, long transport times may mandate EMS use of thrombolytic therapy or early recognition for direct transport to one of the 20% of U.S. hospitals (10% of European hospitals) that can do primary PTCA (42), it seems likely that the TPI would improve care for patients with anterior AMI in such settings; this deserves further study.

The TPI-capable electrocardiographs may be particularly useful in EMS settings. Prehospital administration of thrombolytic therapy has already shown promise (43–46). The new availability of single-bolus thrombolytic therapy (47–49) and the increasing availability of 12-lead ECGs in ambulances (50–54) are providing a foundation for better exploitation of this treatment approach (55–57) Automatic generation in the field of TPI predictions for patients with ST-segment elevation indicative of AMI could support EMS use of thrombolytic therapy. In addition, for patients with contraindications to thrombolysis, prehospital identification by the TPI could obviate transport to a facility without primary PTCA ability, and therefore the need for re-transport to a PTCA-capable center. Clarifying needs and options for reperfusion in the field, especially in rural areas, would save time and thereby improve patient outcomes (58). That the TPI increased overall rates of reperfusion, by either thrombolytic therapy or primary PTCA, suggests that it could facilitate use of reperfusion in prehospital EMS settings.

As an adjunct to real-time clinical use of the TPI, retrospective use of the TPI's predictions for comparison with actual clinical outcomes may be useful in efforts to improve the care of patients with AMI. As a validated, clinically based set of predictive models, using the TPI to make risk-adjusted predictions of expected mortality rates and other outcomes might be more attractive to clinicians than the commonly used risk-adjusted predictions based on medical record review or insurance claims data (59, 60). This is supported by our confirmation of the TPI's very good predictive performance for patients receiving thrombolytic therapy or PTCA (ROC areas, 0.82 to 0.85). Because clinical improvement initiatives based on comparisons of actual and predicted clinical outcomes will succeed only to the degree that physicians accept the validity and fairness of these comparisons, use of the TPI may improve care more than current outcome reports not based on clinically applicable predictive models. Accordingly, it seems reasonable to develop and test outcome reports based on the TPI.

In summary, our results suggest that the TPI is appropriate in a wide range of emergency departments and probably in prehospital EMS settings. It appears to facilitate use of thrombolytic and overall reperfusion therapy, including PTCA, and thus appears adaptive to the current trend of increasing use of PTCA. Further clinical trials should be done where the TPI might particularly benefit care, including rural and EMS settings. Also warranted are studies to understand how the TPI can best be combined with education, real-time support for decision making, and feedback reports to improve treatment of AMI.

APPENDIX

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Cost-Effectiveness Analyses of Colorectal Cancer Screening: A Systematic Review for the U.S. Preventive Services Task Force

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Purpose: **To perform a systematic review of the cost-effectiveness of colorectal cancer screening for the U.S. Preventive Services Task Force.**

Data Sources: **MEDLINE and the British National Health Service Economic Evaluation Database, January 1993 through September 2001.**

Study Selection: **Original economic evaluations of colorectal cancer screening in average-risk patients were reviewed. The authors sought studies addressing the incremental cost-effectiveness of different screening strategies compared with no screening, of different screening strategies compared with one another, and of different ages of screening initiation and cessation. Two investigators independently reviewed each abstract, and potentially eligible articles were retrieved. A four-member working group reached consensus regarding final inclusion or exclusion of articles.**

Data Extraction: **One reviewer extracted data into evidence tables. The results were checked by other members and discrepancies resolved by consensus.**

Data Synthesis: **Among 180 potential articles identified, 7 were retained in the final analysis. Compared with no screening, cost-effectiveness ratios for screening with any of the commonly considered methods were generally between $10 000 and $25 000 per life-year saved. No one strategy was consistently found to be the most effective or to have the best incremental cost-effectiveness ratio. Currently available models provided insufficient evidence to determine optimal starting and stopping ages for screening.**

Conclusions: **Screening for colorectal cancer appears cost-effective compared with no screening, but a single optimal strategy cannot be determined from the currently available data. Additional data regarding adherence with screening over time, complication rates in real-world settings, and colorectal cancer biology are needed. Additional analyses are necessary to determine optimal ages of initiation and cessation.**

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See related articles on pp 129-131 and pp 132-141.

Colorectal cancer is the second leading cause of cancer mortality in the United States, with more than 57 000 deaths expected in 2001 (1). Evidence from several studies suggests that screening for, detecting, and removing colorectal cancer and precancerous adenomatous polyps can reduce the incidence of colorectal cancer and colorectal cancer–related mortality (2). Questions remain, however, about which method or methods of screening should be used, how frequently screening should be performed, and at what ages screening should begin and end. In addition, health care policymakers wish to know not only whether screening is effective but also whether it is cost-effective. Existing clinical trials of colorectal cancer screening have not directly compared different screening approaches and have not tested different starting and stopping ages. In the absence of such data, cost-effectiveness analyses using simulation models may provide the best information for answering such questions (3).

To help inform the U.S. Preventive Services Task Force's deliberation on recommendations regarding screening for colorectal cancer, we examined three questions:

1. What is the cost-effectiveness of colorectal cancer screening by any method compared with no screening?
2. Can we use incremental cost-effectiveness data to determine the relative effectiveness and cost-effectiveness of different screening options and thus determine whether there is a preferred strategy for screening?
3. What is the incremental cost-effectiveness of continuing screening to 85 years of age compared with stopping screening at 70, 75, or 80 years of age? What is the incremental cost-effectiveness of starting screening at 40 or 45 years of age compared with 50 years of age?

METHODS

Search Strategy

The principles and rationale for our approach to conducting systematic reviews of cost-effectiveness studies are described elsewhere (4). We searched MEDLINE and the British National Health Service Economic Evaluation Database (NHS EED) (http://agatha.york.ac.uk/nhsdhp.htm) between January 1993 and September 2001. We exploded the Medical Subject Headings "colorectal neoplasms" and "mass screening." We used different strategies in each database to identify cost-effectiveness analyses. For our MEDLINE search, we added the exploded Medical Subject Heading "costs and cost analysis." In the NHS EED, we limited the search to "economic evaluations." We chose 1993 as a starting point because it was the year in which the first trial establishing strong evidence for the effectiveness of colorectal cancer screening was published (5). To identify studies not captured by our database searches and studies that are ongoing or unpublished, we manually searched the reference lists of retrieved articles and contacted selected authors and experts in the field.

Two investigators reviewed titles and abstracts of publications identified by the literature searches. Using information in the abstracts, we excluded studies that were not cost-effectiveness or cost-utility analyses, including other types of economic evaluations that did not quantify the health outcomes achieved for a given cost; studies that reported only cost per patient screened, cost per cancer detected, or cost per death prevented; studies that did not contain original analyses; articles that did not address at least one of our three questions of interest; studies performed from perspectives other than the societal perspective or the perspective of public third-party payers; and studies that used cost or disease incidence estimates from outside the United States. When we encountered multiple publications that reported results from the same cost-effectiveness model, we included the most comprehensive analysis and used other papers for supplemental information. When the decision about whether to include a study could not be made by reading the title or abstract, we evaluated the full article. Disagreements on study inclusion were resolved by consensus of the authors.

All authors reviewed each included article. Reviews focused on the assumptions of each study regarding the epidemiology and natural history of colorectal cancer; estimates of variables related to the effectiveness of screening, including test accuracy, adherence rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of cancer cases and cancer deaths prevented by screening; and the effect of varying key variables (sensitivity analyses).

For each study, we used available data to tabulate life-years gained and costs per person for each of the major strategies under consideration: annual fecal occult blood testing, sigmoidoscopy every 5 years, combination of annual fecal occult blood testing and sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, and colonoscopy (every 10 years, at 55 and 65 years of age, or once in a lifetime). The evaluated strategies were arrayed in order of effectiveness. Costs were updated to U.S. dollars in 2000 by using the Consumer Price Index for medical care.

If one strategy was more costly and less effective than another strategy, it was considered to be strongly dominated. If a strategy was both less effective and had a higher cost-effectiveness ratio than another strategy, it was considered to be weakly dominated. Incremental cost-effectiveness ratios were then calculated for all nondominated strategies by using the following formula: (costs strategy 2 − costs strategy 1)/(life-years gained with strategy 2 − life-years gained with strategy 1).

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Context

It is unclear which colorectal cancer screening strategy is most cost-effective.

Contribution

On behalf of the U.S. Preventive Services Task Force, the authors reviewed seven published analyses that addressed the cost-effectiveness of fecal occult blood testing (single or annual), flexible sigmoidoscopy every 5 years alone or with fecal occult blood testing, barium enema every 5 years, and colonoscopy every 10 years.

The screening strategies all cost $10 000 to $25 000 per year of life saved.

Implications

Physicians should discuss the advantages and disadvantages of the various colorectal cancer screening strategies with their patients to decide which test is best for each individual.

–The Editors

RESULTS

Identification of Cost-Effectiveness Analyses

Our initial searches identified 180 potentially relevant studies. On initial review of titles and abstracts, we excluded 159 articles that were clearly not related to our topic of interest. Of the 21 full articles retrieved and reviewed by the investigators, six met the inclusion criteria. **Appendix Table 1** (available at www.annals.org) shows the reasons for exclusion of the remaining articles.

Through supplemental searches, we identified two additional studies that met our inclusion criteria. One was identified through manual searching of the reference lists of retrieved articles (6), and the other was identified through contact with experts but was subsequently published and indexed in MEDLINE (7). Because the book chapter by Wagner and colleagues (6) was the most comprehensive description of the model developed by the Office of Technology Assessment, we used it rather than the more recent analysis by Glick (7).

Study Descriptions

Table 1 shows the basic features of the included analyses. All but one were cost-effectiveness analyses that expressed benefits in days of life or life-years gained and costs in U.S. dollars. One study presented results in cost per quality-adjusted life-year gained (13). Each study considered one or more alternative means of screening in addition to the option of no screening. The perspective of the analyses was societal or that of a third-party payer. All studies considered direct costs, including the costs of screening, diagnostic tests, and treatment; no studies considered patient time costs associated with attendance for screening, diagnostic, or surveillance procedures or for treatment of cancer.

Table 1. **Study Characteristics***

Characteristic	**Study, Year (Reference)**		
	Wagner et al., 1996 (6)	**Frazier et al., 2000 (8)**	**Khandker et al., 2000 (9)**
Model type	Unknown	Markov	Dynamic state transition
Perspective	Societal	Societal	Unknown (appears to be societal)
Age range for screening, *y*	50–85	50–85	50–85
Time horizon	Lifetime	Lifetime	35 years
Key biological assumptions			
Cancer from adenomas, %	70	100	100
Polyp dwell time, *y*	10	NR	Variable
Time from early to late cancer, *y*	2 (2 from late disease to symptoms)	NR	5
Additional features			
Relevant interventions considered	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years BE every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years BE every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years FOBT + FS, annually + every 5 years BE every 5 years Colonoscopy every 10 years
Discount rate, %	5	3	3
Was adherence modeled?	No	Yes	Yes (2 scenarios)
How were benefits measured?	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment
Adverse effects			
Source of harms data	Systematic review	2 articles	Unclear
Perforation rate for colonoscopy (with polypectomy), %	0.07 (NR)	NR	0.85†
Bleeding rate for colonoscopy (with polypectomy), %	NR	NR	NR
Deaths for colonoscopy per 100 000 examinations (range), *n*	5 (NR)	5 (0.5–50)	23.6 (12–35)
Costs			
Types of costs included	Direct	Direct	Direct
Sources of cost information	Medicare reimbursement data	Data from large HMO	Medicare and survey of private payers
Cost of colonoscopy (cost with polypectomy), $	285 (434)	1012 (1519)	438–670 (702–981)
Cost of FOBT, $	10	38	7.50–10
Cost of sigmoidoscopy, $	80	279	94–175
Cost of care for perforation (cost of care for bleeding), $	35 000	NR	28 200
Cost of cancer care, $	Early: 35 000 Late: 45 000	Local: 22 000 Regional: 43 900 Distant: 58 300	Local: 49 587 Regional: 79 857 Distant: 60 180
Measured in U.S. dollars from what year?	1995	1998	1994
Relevant intermediate outcomes			
Sensitivity of a single test for detection of cancer (detection of large polyps), %	FOBT: 40–60 (10)	FOBT: 33 (10) FS: 95 BE: 70 (50) Colonoscopy: 95	FOBT: 60 (10) FS: NR BE: 84 (82) Colonoscopy: 97 (85)
Polyps and cancer reachable by sigmoidoscopy, %	50	Variable	70
Reduction in mortality with screening, %	FOBT: 28 FS: NR FOBT + FS: NR BE: NR Colonoscopy: NR	FOBT: 55 FS: 40 FOBT + FS: 71 BE: 47 Colonoscopy: 64	FOBT: 80 FS: 69 FOBT + FS: 88 BE: 89 Colonoscopy: 90
Proportion of colorectal cancer cases prevented during course of program, %	NR	FOBT: 39 FS: 37 FOBT + FS: 60 BE: 38 Colonoscopy: 58	FOBT: 60 FS: 66 FOBT + FS: 80 BE: 86 Colonoscopy: 86
Important variables in sensitivity analysis	Polyp dwell time	Death due to colonoscopy	Polyp dwell time, adherence, cost of colonoscopy

* BE = barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; HMO = health maintenance organization; NA = not available; NR = not reported; QALY = quality-adjusted life-year; SEER = Surveillance, Epidemiology, and End Results.

† Rate of any complication.

Table 1—Continued

Study, Year (Reference)			
Sonnenberg et al., 2000 (10)	**Vijan et al., 2001 (11)**	**Loeve et al., 2000 (12)**	**Ness et al., 2000 (13)**
Markov	Markov	Microsimulation model	Discrete-event stimulation and cost-utility analysis
Third-party payer	Third-party payer	Unknown	Unknown
50–death	50–85	50–75	Single screening
Lifetime	Lifetime	Lifetime	Lifetime
100	75	100	100
NR	10 years	20 years	2 groups: one with mean of 26 years, other with mean of 52 years
NR	2 in localized disease, 1 in regional disease	5.3	5.55
Annual FOBT FS every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years Colonoscopy at 50 and 60 years of age	FS every 5 years between 50 and 75 years of age	Single colonoscopy at 45–50, 50–54, 55–59, or 60–64 years of age
3	3	3	3
Yes	Yes	No	No
Costs per life-year saved; most benefit from prevention; early detection reduces mortality by 18%	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Net costs per person and life-years gained per 1000 persons	Cost per QALY saved
2 articles	2 articles	Nonsystematic reviews	Multiple studies
0.2 (0.38)	0.1 (NR)	0.2 (NR)	0.1 (NR)
0.15 (2.0)	NR	NR	NR (0.3)
10 (NR)	7.5 (0–30)	NR	20 (NR)
Direct	Direct	Direct	Direct
Medicare cost data from 1998	Data from Medicare and Kaiser Permanente	Estimates based on published literature	Medicare rates and previous studies
695 (1003)	550 (765)	300 (400)	303 (530)
3.50	17	NA	NA
400	225	100	NA
13 000 (4360)	20 000	30 000	NR
45 228	Local: 60 000 Regional: 82 800 Distant: 73 000	Initial 25 000 over 6 months Ongoing 2200/year Terminal: 16 000 over 6 months	Initial Local: 16 051 Regional: 18 457 Distant: 21 093 Ongoing Local: 425/year Regional: 1944/year Distant: 21 209 Terminal: 16 722
2000	1999	1993	1998
FOBT: 40 (NR)	FOBT: 30 local, 50 regional (5)	Colonoscopy: 95 (95)	Colonoscopy: 95 (85)
45	55	Unknown	NA
FOBT: 18 FS: 34 FOBT + FS: NR BE: NR Colonoscopy: 90	FOBT: 52 FS: 44 FOBT + FS: 70 BE: NR Colonoscopy: 75	55	Men: 68 Women: 65
FOBT: 16 FS: 34 FOBT + FS: NR BE: NR Colonoscopy: 75	FOBT: 60 FS: 66 FOBT + FS: 70 BE: 86 Colonoscopy: 86	47	Men: 64 Women: 61
Adherence	Adherence	Dwelling time distribution, mean dwelling time	NR

Table 2. **Cost-Effectiveness Ratios of Various Tests for Colorectal Cancer Compared with No Screening***

Test	Study, Year (Reference)				
	Wagner et al., 1996 (6)	Frazier et al., 2000 (8)	Khandker et al., 2000 (9)	Sonnenberg et al., 2000 (10)	Vijan et al., 2001 (11)
Annual FOBT, $	11 725	17 805	13 656	10 463	5691
FS every 5 years, $	12 477	15 630	12 804	39 359	19 068
Annual FOBT + FS every 5 years, $	13 792	22 518	18 693		17 942
DCBE every 5 years, $	11 168	21 712	25 624		
Colonoscopy every 10 years, $	10 933	21 889	22 012	11 840	9038

* All costs are updated to U.S. dollars in 2000. DCBE = double-contrast barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.

In general, each model used data on the incidence of colorectal neoplasms (adenomatous polyps and cancer) to simulate the natural history of disease in a cohort of adults at average risk, typically those between 50 and 85 years of age. These neoplasms were subject to detection and removal by the different screening strategies as they progressed from adenomas to early-stage cancer and then to late-stage cancer. Survival after detection was generally considered to be stage-related. The costs and complications of screening and treatment were modeled with various degrees of precision.

Benefits and costs were discounted at 3% or 5% in the base-case analyses. Sensitivity analyses were used to examine uncertainty about the variables used to build the models. Most sensitivity analyses were one-way, although some studies examined the effect of setting several variables to the most pessimistic levels. Factors that caused cost-effectiveness ratios to vary more than twofold in sensitivity analyses were polyp dwell time, the proportion of cancer arising from adenomas, adherence rates, and the cost and adverse effects of colonoscopy.

The effectiveness of screening in preventing colorectal cancer and cancer deaths also varied considerably. The analysis by Khandker and associates (9) was the most optimistic: Most strategies prevented more than 60% of cases of cancer and 80% of colorectal cancer deaths. Frazier and colleagues' analysis produced the smallest reductions (8), whereas Vijan and coworkers (11) found reductions in incidence similar to those of Khandker and associates and mortality reductions similar to Frazier and colleagues. The analyses by Loeve and associates (12) and Ness and colleagues (13) were intermediate. The model of Sonnenberg and coworkers (10) produced the lowest estimates of efficacy for fecal occult blood testing and for sigmoidoscopy, but their estimate for the efficacy of colonoscopy was among the highest.

Question 1: Cost-Effectiveness of Screening for Colorectal Cancer with Any Method Compared with No Screening

All studies found that screening for colorectal cancer by any of the included screening strategies reduced deaths from colorectal cancer in adults older than 50 years of age who were at average risk for colorectal cancer. Table 2 shows cost-effectiveness ratios for analyses that examined two or more of the most commonly evaluated strategies: fecal occult blood testing annually, flexible sigmoidoscopy every 5 years, a combination of fecal occult blood testing and sigmoidoscopy, barium enema every 5 years, and colonoscopy every 10 years, each compared with no screening. In base-case analyses, most strategies had average cost-effectiveness ratios, ranging from $10 000 to $25 000 per year of life saved. Among the studies examining single methods of screening, the analysis by Loeve and colleagues found sigmoidoscopy to be cost saving when relatively optimistic cost values were used and the time range for the analysis was extended beyond 35 years (12). Ness and associates found that screening adults with colonoscopy between 50 and 54 years of age had a cost-effectiveness ratio of less than $10 000 per life-year saved (13).

Although the results of the different studies are relatively consistent, the base-case assumptions about the effectiveness or costs of screening for colorectal cancer may have been overly optimistic. Alternative sensitivity analyses that assumed "worst-case" scenarios about the biological behavior of neoplasms and effectiveness of treatment generally produced cost-effectiveness ratios of less than $100 000 per life-year saved.

Question 2: Use of Incremental Cost-Effectiveness Data To Determine the Relative Effectiveness and Cost-Effectiveness of Different Screening Options and the Preferred Screening Strategy

Five studies we identified examined multiple screening strategies (annual fecal occult blood testing, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, colonoscopy every 10 years, and the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years) and reached heterogeneous conclusions about their effectiveness and incremental cost-effectiveness (**Table 3**; **Appendix Table 2** [available at www.annals.org]).

With regard to the most effective strategy, defined as that yielding the greatest average number of life-years gained, the analyses by Wagner (6), Frazier (8), and Vijan (11) and their colleagues found the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years to be most effective. Khandker and associates (9) and Sonnenberg and coworkers (10) found colonoscopy every 10 years to be the most effective, although the latter researchers did not consider the combination of fecal occult blood testing and sigmoidoscopy. Of note, four of five multiple-strategy analyses found fecal occult blood testing alone to be more effective than sigmoidoscopy alone for reduction of deaths from colorectal cancer (6, 8, 9, 11).

The most "cost-effective" strategy depends on the cost threshold beyond which one no longer wishes to "pay" for additional years of life saved. If it is assumed that one does not wish to pay more than $20 000 per life-year saved, the five studies reached heterogeneous conclusions about the best strategy. At least one analysis found annual fecal occult blood testing, sigmoidoscopy every 5 years, or colonoscopy every 10 years to be the optimal method of screening. As one's willingness to pay to save more life-years increases, colonoscopy every 10 years or the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years becomes favored.

Factors That Affect Cost-Effectiveness Results

Several important variables differed across the five multiple-strategy analyses and may explain some of the variability in incremental cost-effectiveness ratios (Table 1). However, we could not identify a single variable as being solely responsible for the heterogeneity in the outcomes we detected.

Assumptions about the biological behavior of colorectal cancer are important factors in the ability of the model to accurately simulate real life. Assumptions about the proportion of cancer arising from adenomas are particularly important because screening strategies that work mostly by preventing cancer through the removal of polyps, such as screening colonoscopy, appear to be most effective when it is assumed that all cancer arises from detectable adenomas (8, 11).

Similarly, the duration of the precancerous and early cancer detectable phases (dwell time) affects the relative rank of screening strategies. If the dwell time is long, strategies that involve a highly accurate test at a less frequent interval (for example, screening colonoscopy every 10 years) will appear to perform well compared with a more frequent but less accurate test, such as annual fecal occult blood testing.

Screening adherence is another important factor. No analysis was completely successful in simulating actual patterns of adherence. In all models, the adherence level was changed for all tests equally, an assumption that may not be correct (for example, adherence may differ for fecal occult blood testing and colonoscopy). This assumption of equal adherence among methods again favors the more accurate but more onerous screening methods, such as colonoscopy, particularly when adherence is assumed to be low.

Most of the analyses assumed that survival was based on the stage at diagnosis and estimated stage-specific survival from the National Center of Health Statistics and Surveillance Epidemiology and End Results Survey (14). Of note, Sonnenberg and coworkers made the very conservative assumption that cancer detected early by screening would produce a mortality rate only 18% lower than that detected clinically (10). This assumption makes fecal occult blood testing appear much less effective than a method that relies more on detection and removal of polyps, such as colonoscopy.

Modeling of adverse effects also influences the cost-effectiveness of different strategies. The adverse effects of colorectal cancer screening are mainly those associated with complications of colonoscopy (whether initially for screening or as part of the "diagnostic cascade" after positive results on another screening test), which include perforation; bleeding; or, rarely, death. Studies that fail to model all adverse consequences of colonoscopy will overestimate cost-effectiveness and will favor screening colonoscopy over strategies that involve fewer colonoscopic examinations.

All studies included only the direct costs of screening. No study examined the cost of patient time missed from work for screening and treatment. The effect of considering such costs on the relative cost-effectiveness of each method is unclear: Colonoscopy would have higher patient

Table 3. **Preferred Strategy at Different Levels of "Acceptable" Costs per Life-Year Saved***

Study, Year (Reference)	Most Effective Strategy†	Preferred Strategy If Willing to Pay‡			
		<$20 000 per Life-Year Saved	$20 000–$30 000 per Life-Year Saved	$30 000–$50 000 per Life-Year Saved	$50 000–$100 000 per Life-Year Saved
Wagner et al., 1996 (6) (alternative)§	FOBT + FS	Colonoscopy every 10 years	Colonoscopy every 10 years	FOBT + FS	FOBT + FS
Frazier et al., 2000 (8)	FOBT + FS	Annual FOBT	Annual FOBT	FOBT + FS	FOBT + FS
Khandker et al., 2000 (9)	Colonoscopy every 10 years	FS every 5 years	FS every 5 years	Annual FOBT	Colonoscopy every 10 years
Sonnenberg et al., 2000 (10)	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years
Vijan et al., 2001 (11)	FOBT + FS	Annual FOBT	Annual FOBT	Colonoscopy at 55 and 65 years of age only	Colonoscopy at 55 and 65 years of age only

* FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.
† Most effective strategy = largest number of life-years saved among 5 main strategies.
‡ All costs are updated to U.S. dollars in 2000.
§ Using sensitivity of 50% for double-contrast barium enema, rather than 70% used in base case.

costs per test but would be required less frequently than other methods. Overall, the cost per life-year saved would probably increase for all methods.

Another important factor is the way in which each analysis models postpolypectomy surveillance for new adenomas and cancer. Studies differed with respect to the interval for repeating colonoscopy after detection and removal of a clinically significant adenomatous polyp. Wagner and colleagues assumed that all patients with adenomatous polyps would undergo surveillance colonoscopy every 4 years and that none of these patients would develop additional polyps or cancer and would die of other causes (6). Frazier and associates assumed that all patients with a "high-risk polyp" (>1 cm in size or having villous histology) would undergo surveillance colonoscopy every 3 years until 85 years of age or death (8). Khandker and coworkers used a more complicated model in which after an initial polyp larger than 1 cm in size was detected, an initial surveillance colonoscopy was performed at 3 years and subsequent follow-up studies were performed every 5 years if polyps were detected on the previous examination (9). In that study, it appears that regular screening was reinitiated if colonoscopy results were negative, but the documentation was unclear on this point. Sonnenberg and colleagues modeled surveillance colonoscopy 3 years after polyp detection but allowed screening to be suspended for 10 years after negative results on colonoscopy (10). Vijan and associates (11) also modeled initial surveillance colonoscopy 3 years after detection of a large adenoma (>1 cm) and lengthened the interval for future surveillance examinations to every 5 years after negative results on examination. More aggressive programs with more frequent examination can increase effectiveness in preventing future cancer but will increase complications and costs.

Question 3: Incremental Cost-Effectiveness of Continuing Screening to 85 Years of Age Compared with Stopping Screening at 70, 75, or 80 Years of Age, or of Starting Screening at 40 or 45 Years of Age Compared with 50 Years of Age

Ness and colleagues (13) examined different ages at which to perform one-time screening colonoscopy and found that for women, screening between 45 and 49 years of age was dominated by one-time screening between 50 and 54 years of age. For men, screening at 45 to 49 years of age compared with screening from 50 to 54 years of age was associated with a cost of $69 000 per quality-adjusted life-year gained. An older study by Eddy (15) found that starting annual fecal occult blood testing at 40 years of age added less than 1 day of average life expectancy and increased costs per person screened almost twofold compared with starting at 50 years of age.

We found no studies that examined the incremental cost-effectiveness of different stopping ages, although Rich and Black (16) used life-table analyses to suggest that by 75 years of age, 68% of the potential mortality reduction from initiating fecal occult blood testing at 50 years of age had been achieved. If screening were continued to 80 years of age, 83% of the potential reduction in mortality would be achieved.

DISCUSSION

Our systematic review identified seven high-quality cost-effectiveness analyses; five examined multiple colorectal cancer screening strategies, and two examined single strategies. Compared with no screening, all seven analyses found that any of the common screening strategies for adults 50 years of age or older will reduce mortality from colorectal cancer. The cost per life-year saved for colorectal cancer screening ($10 000 to $25 000 for most strategies compared with no screening) compares favorably with other commonly endorsed preventive health care interventions, such as screening mammography for women older than 50 years of age or treatment of moderate hypertension.

Whether one method of colorectal cancer screening is superior to other methods is not clear from these analyses. Many observers have interpreted recent studies (17–19) documenting the relative greater single-test accuracy of colonoscopy compared with sigmoidoscopy, fecal occult blood testing, or double-contrast barium enema for detection of colorectal cancer or adenomas as proof that colonoscopy should be the screening method of choice for colorectal cancer (20). The five multiple-strategy analyses that we identified, however, did not uniformly find that colonoscopic screening was the most effective or cost-effective strategy. The most effective strategy tended to be colonoscopy every 10 years or the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years. The most "cost-effective" strategy identified depended on the level of incremental cost-effectiveness considered to be worthwhile and was not conclusive.

The differences in effectiveness, and hence cost-effectiveness, among the models are related to different assumptions each model makes about the biological behavior of colon cancer, the effectiveness and adverse effects associated with each strategy, and the likelihood that patients will actually complete the tests required for any given strategy. Because the limited available empirical data cannot tell us which set of assumptions is most accurate, we cannot definitively state the most effective or cost-effective strategy for screening. We can say with confidence, however, that any of the methods are effective compared with no screening for adults 50 years of age or older.

Other reviewers have recently examined the literature on the cost-effectiveness of screening for colorectal cancer. Brown and Knopf (21) reviewed cost-effectiveness analyses completed by 1998 and identified four studies for inclusion (6, 12, 15, 22). As with our analysis, they concluded that screening by any of several methods was cost-effective compared with no screening but that the available evidence could not determine the most effective strategy. McMahon and colleagues recently published a reanalysis of four previous cost-effectiveness analyses (23). They included the studies by Eddy (15) and Wagner and coworkers (6) that were examined by Brown and Knopf, as well as Glick's reanalysis (7) of Wagner and coworkers' model. They recalculated incremental cost-effectiveness ratios for the methods considered and concluded that double-contrast barium enema every 3 years or the combination of double-contrast barium enema every 5 years plus fecal occult blood testing annually were the most effective strategies. However, these conclusions were limited by the overly optimistic estimates (compared with data from the best subsequent empirical study [19] of double-contrast barium enema sensitivity and specificity) used in the four analyses that McMahon and colleagues included.

We did not find sufficient evidence about starting and stopping ages for screening to provide useful information for making recommendations. The analyses by Ness and associates (13) and Eddy (15) suggest that the benefits of starting screening at 40 or 45 years of age were small and costly compared with starting at 50 years of age, but further analyses with a range of tests are required. The cost-effectiveness of different stopping ages for screening also was not well examined and may differ substantially depending on the health of the patient being considered for screening (24).

Some potential limitations should be considered in interpreting our results. All but one of our analyses examined cost per life-year gained and did not account for differences in quality of life associated with undergoing screening, surveillance, or treatment for cancer. Differences in model structure, data inputs for key variables, and regimens evaluated limited our ability to draw definitive conclusions about the most effective and cost-effective tests. It is difficult to determine from the data presented in each report whether differences in the results obtained relate mainly to differences in the variables used or in the model structures. We considered only strategies that involved one kind of test (or a pair of tests) and repeated those tests at some regular interval. More complex strategies, including ones that screen younger persons with one test and then switch to a different test at older ages, have not been evaluated. Uncertainty about estimates for different variables was addressed in each study by one-way sensitivity analyses or by testing a set of "optimistic" or "pessimistic" assumptions, but only one of the studies provided probabilistic ranges for its results. Finally, our findings apply only to screening patients at average risk for colorectal cancer; screening higher-risk patients may be even more cost-effective.

Some modelers attempted to validate their models by comparing their results with results of empirical screening trials (6, 8, 11). It would be valuable to have the creators of the different models participate in a validation exercise to compare intermediate and long-term model outcomes by using one common set of variables for a common set of strategies. In this manner, we could confirm that the relative ranking of strategies is similar and not dependent on model structure and assumptions. Nonetheless, the consistent finding that any form of screening is superior to no screening supports the general conclusion that any of the commonly considered strategies are reasonable alternatives.

Our review has important implications for future research and policymaking. It supports the consensus view among major policymaking bodies that screening for colorectal cancer in some form is warranted for adults at average risk who are older than 50 years of age. It also shows that current evidence is insufficient to determine the most effective or cost-effective strategy for screening or to determine the optimal starting and stopping ages for screening. Because no single method of screening is clearly superior to another, patient preferences can play an important role in deciding how screening should be performed (25). Finally, our findings suggest that further research about the natural history of colorectal cancer; the effect of screening, surveillance, and treatment on quality of life; the real-world incidence of complications of screening; and longitudinal data about adherence with different screening strategies in unselected populations could help clarify some of the uncertainty about relative test performance.

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Current author addresses, author contributions, and Appendix Tables and their associated references are available at www.annals.org.

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BRIEF COMMUNICATION

Safety and Efficacy of Liposomal Amphotericin B Compared with Conventional Amphotericin B for Induction Therapy of Histoplasmosis in Patients with AIDS

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Background: In patients with moderate to severe histoplasmosis associated with AIDS, the preferred treatment has been the deoxycholate formulation of amphotericin B. However, serious side effects are associated with use of amphotericin B.

Objective: To compare amphotericin B with liposomal amphotericin B for induction therapy of moderate to severe disseminated histoplasmosis in patients with AIDS.

Design: Randomized, double-blind, multicenter clinical trial.

Setting: 21 sites of the U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group.

Patients: 81 patients with AIDS and moderate to severe disseminated histoplasmosis.

Measurements: Clinical success, conversion of baseline blood cultures to negative, and acute toxicities that necessitated discontinuation of treatment.

Results: Clinical success was achieved in 14 of 22 patients (64%) treated with amphotericin B compared with 45 of 51 patients (88%) receiving liposomal amphotericin B (difference, 24 percentage points [95% CI, 1 to 52 percentage points]). Culture conversion rates were similar. Three patients treated with amphotericin B and one treated with liposomal amphotericin B died during induction ($P = 0.04$). Infusion-related side effects were greater with amphotericin B (63%) than with liposomal amphotericin B (25%) ($P = 0.002$). Nephrotoxicity occurred in 37% of patients treated with amphotericin B and 9% of patients treated with liposomal amphotericin B ($P = 0.003$).

Conclusion: Liposomal amphotericin B seems to be a less toxic alternative to amphotericin B and is associated with improved survival.

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* For a list of study investigators and numbers of patients enrolled, see Appendix.

In endemic areas, 5% to 20% of HIV-infected persons develop disseminated histoplasmosis (1–3). Amphotericin B is the therapeutic agent of choice for induction therapy of moderate to severe disseminated histoplasmosis (1), whereas noncomparative studies show that itraconazole (4) and fluconazole (5, 6) are effective for induction and consolidation treatment of milder disease. Treatment of severe disease with amphotericin B, however, has not produced optimal results (3).

Liposomal amphotericin B achieves high concentrations in the reticuloendothelial system (7) and is less nephrotoxic. It achieves higher blood concentrations and exhibits reduced clearance compared with deoxycholate amphotericin B and other lipid preparations (8). In addition, it achieves the highest concentrations in the brains of rabbits (9). Central nervous system involvement indicates poor outcome in patients with AIDS and disseminated histoplasmosis (2, 10). We compared the safety and efficacy of liposomal amphotericin B with deoxycholate amphotericin B for treatment of moderate to severe disseminated histoplasmosis in persons with AIDS.

METHODS

Study Design

After we obtained informed consent, patients with AIDS and moderate to severe disseminated histoplasmosis were randomly assigned in a 2:1 ratio (liposomal amphotericin B–amphotericin B) in this multicenter double-blind trial. Randomization blocks of size 3 were used, and the research pharmacist at each site randomly assigned patients using the closed-envelope (security) technique. Disseminated histoplasmosis was diagnosed by culture of *Histoplasma capsulatum*, by histopathologic examination, or by urine or serum antigen levels determined by enzyme immunoassay (11, 12). Patients were excluded from the trial if they had a serum creatinine level greater than twice the upper limit of normal; had other uncontrolled opportunistic infections or malignant disease; or had been treated for 3 or more days with ketoconazole, itraconazole, fluconazole, or amphotericin B.

Medication Administration

Patients received daily doses of liposomal amphotericin B (AmBisome, Fujisawa Healthcare, Deerfield, Illinois), 3.0 mg/kg of body weight, or amphotericin B, 0.7 mg/kg, for 2 weeks. Medication was administered in a blinded fashion by intravenous infusion over 2 hours. Patients in whom induction therapy was successful received itraconazole for 10 weeks as consolidation therapy. Premedication was not allowed before the first dose. For later doses, premedication could be used and infusion times could be modified depending on side effects.

Monitoring

Before random assignment, a history and physical examination was performed and hematologic and serum

Context

Amphotericin B is the preferred initial treatment for moderate to severe disseminated histoplasmosis. Because amphotericin B has many serious side effects, alternative treatments are needed.

Contribution

This double-blind, multicenter trial compared liposomal amphotericin B with regular amphotericin B in patients with disseminated histoplasmosis and AIDS. Liposomal amphotericin B had a higher treatment response (88% vs. 64%) and lower mortality rates (2% vs. 13%). It also had fewer infusion-related side effects (25% vs. 63%) and less nephrotoxicity (9% vs. 37%).

Implications

Although expensive, liposomal amphotericin B is better than regular amphotericin B for treating severe disseminated histoplasmosis.

–The Editors

chemistry values, serum and urine samples for detecting *H. capsulatum* antigen levels, quantitative lysis centrifugation blood cultures, and a chest radiograph were obtained. Samples were drawn for blood cultures and serum and urine antigen testing for *H. capsulatum* on days 4, 7, and 14 and at weeks 4, 8, and 12 (or when a patient withdrew from the study). Samples were analyzed at the Histoplasmosis Reference Laboratory in Indianapolis, Indiana.

Response Criteria

Clinical and mycologic successes were the primary efficacy end points. A successful clinical response to induction therapy was defined as a maximum daily temperature lower than 37.8 °C for 72 hours; no increase in severity of signs, symptoms, or laboratory abnormalities attributable to histoplasmosis; and the resolution of at least one of the signs or symptoms of histoplasmosis that qualified the patient for enrollment in the trial. A clinical success could be declared after as few as 7 days of induction therapy, at which time itraconazole therapy could be started. A successful clinical outcome after consolidation therapy was defined as resolution or reduction in clinical severity of symptoms and signs attributed to histoplasmosis compared with baseline. Survival was compared for the two treatments. Early discontinuation of induction therapy due to drug toxicity was the primary end point for safety.

Secondary end points were time to defervescence; mycologic efficacy, defined as rate of blood culture conversion; change in *H. capsulatum* antigen levels in urine and serum at week 2; and rates of acute infusion toxicities and nephrotoxicity (increase in serum creatinine level to more than twice the baseline level).

Statistical Analysis

The accrual target was 75 patients. Positive baseline blood cultures were estimated at 80%. The response rate for both therapies was expected to be 70%. Outcome analysis was performed on an intention-to-treat basis. Treatment groups were compared by using the Kruskal–Wallis test for ordered measurements (13) and the Fisher exact test for categorized measurements with corresponding exact 95% CIs (14). Mantel–Haenszel methods were used in a post hoc analysis to assess the impact of enrolling-site differences on clinical outcome (15). The Kaplan–Meier method was used in survival and defervescence analyses, and the treatment groups were compared by using the log-rank test (16). We used StatXact 4 for Windows (Cytel Software, Cambridge, Massachusetts) for efficacy comparisons that involved exact methods. We used SAS software,

Figure 1. **Flow of patients through the study.**

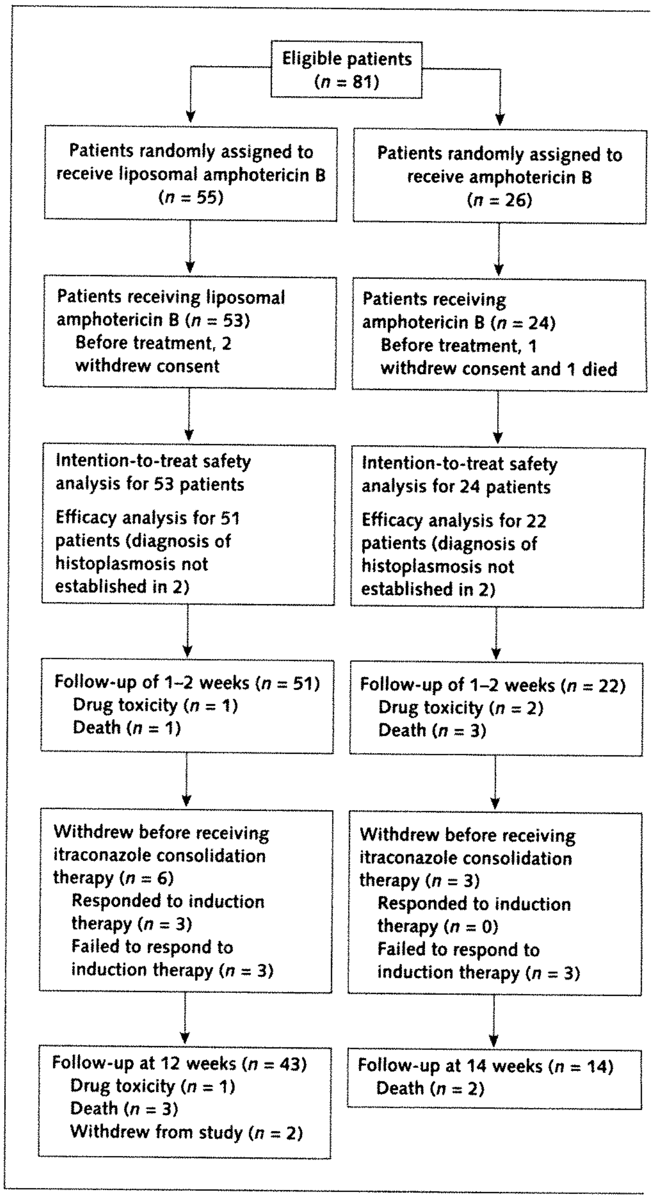

Eligible patients (n = 81)
Patients randomly assigned to receive liposomal amphotericin B (n = 55)
Patients randomly assigned to receive amphotericin B (n = 26)
Patients receiving liposomal amphotericin B (n = 53)
Before treatment, 2 withdrew consent
Patients receiving amphotericin B (n = 24)
Before treatment, 1 withdrew consent and 1 died
Intention-to-treat safety analysis for 53 patients
Efficacy analysis for 51 patients (diagnosis of histoplasmosis not established in 2)
Intention-to-treat safety analysis for 24 patients
Efficacy analysis for 22 patients (diagnosis of histoplasmosis not established in 2)
Follow-up of 1–2 weeks (n = 51)
Drug toxicity (n = 1)
Death (n = 1)
Follow-up of 1–2 weeks (n = 22)
Drug toxicity (n = 2)
Death (n = 3)
Withdrew before receiving itraconazole consolidation therapy (n = 6)
Responded to induction therapy (n = 3)
Failed to respond to induction therapy (n = 3)
Withdrew before receiving itraconazole consolidation therapy (n = 3)
Responded to induction therapy (n = 0)
Failed to respond to induction therapy (n = 3)
Follow-up at 12 weeks (n = 43)
Drug toxicity (n = 1)
Death (n = 3)
Withdrew from study (n = 2)
Follow-up at 14 weeks (n = 14)
Death (n = 2)

Table. **Characteristics of Patients with Progressive Disseminated Histoplasmosis and AIDS, according to Treatment Group**

Variable	Liposomal Amphotericin B Group (*n* = 51)	Amphotericin B Group (*n* = 22)	*P* Value
Median CD4 cell count (range), × 10^9 *cells/L*	0.018 (0.001–0.182)	0.018 (0.004–0.094)	>0.2
Median lactate dehydrogenase value (range), *U/L*	10.34 (0.10–111.17)	16.82 (2.39–124.58)	0.14
Positive blood cultures for *Histoplasma capsulatum, n (%)*	37 (73)	17 (77)	>0.2
Positive bone marrow cultures for *H. capsulatum, n (%)*	8 (16)	3 (14)	>0.2
Positive levels of serum histoplasmosis antigen, *n/n (%)**	38/46 (83)	18/19 (95)	>0.2
Positive levels of urine histoplasmosis antigen and other laboratory findings of histoplasmosis at baseline, *n/n (%)**	39/45 (87)	20/21 (95)	>0.2
Only a positive level of urine histoplasmosis antigen at baseline, *n/n (%)**	4/45 (9)	4/21 (19)	>0.2
Temperature ≥39 °C, *n (%)*	28 (55)	13 (59)	0.19
Hypotension (systolic blood pressure <90 mm Hg), *n (%)*	6 (12)	4 (18)	>0.2
Hypoxia (≤70 mm Hg), *n (%)*	4 (8)	3 (14)	>0.2
Lost >5% of total body weight	33 (65)	5 (68)	>0.2
Karnofsky performance status score <70, *n (%)*	30 (59)	9 (41)	0.08
Bone marrow suppression, *n (%)*†	31 (61)	14 (64)	0.20
Liver function abnormalities, *n (%)*‡	14 (27)	10 (45)	0.07
Central nervous system, gastrointestinal, or adrenal histoplasmosis	4 (8)	2 (9)	>0.2
Coagulopathy, *n (%)*	5 (10)	1 (5)	>0.2
Albumin level <35 g/L, *n (%)*	13 (26)	6 (27)	>0.2

* Antigen levels were determined by using enzyme immunoassay.

† Bone marrow suppression was defined as follows: hemoglobin <100 g/L, absolute neutrophil count <1.0 × 10^9 cells/L, or platelet count <100 × 10^9 cells/L.

‡ Liver function abnormalities were serum levels of alanine and aspartate aminotransferase >2.5 times normal or bilirubin levels >2 times normal.

version 6.12 (SAS Institute, Inc., Cary, North Carolina) for all other analyses.

Role of the Funding Source

This study was supported by a research grant from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Center for Research Resources, and by Gilead Sciences, Inc. The NIAID assisted in the collection, analysis, and interpretation of the data and in the decision to submit the paper for publication. The National Center for Research Resources assisted with data collection at sites with a General Clinical Research Center. Gilead Sciences, Inc. had no direct role in the conduct of this study.

RESULTS

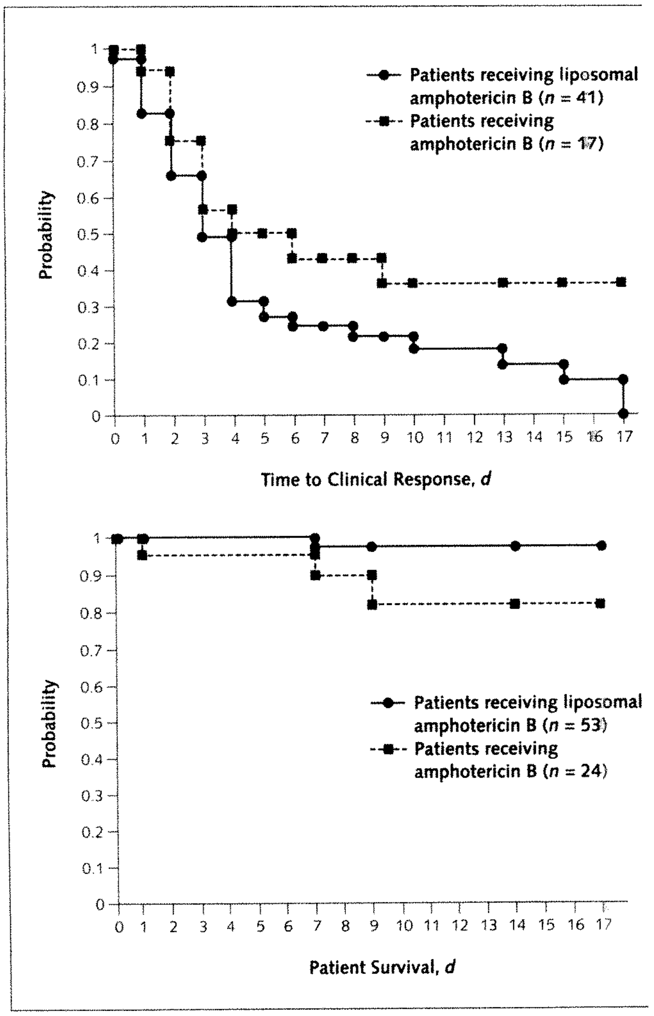
Eighty-one patients were enrolled by 21 sites. Flow of patients through the study is shown in **Figure 1**. Of 55 patients randomly assigned to receive liposomal amphotericin B, 2 withdrew consent before receiving the study medication and were ineligible for the efficacy and safety analyses and 2 were excluded from the efficacy analysis because they did not have disseminated histoplasmosis. Of 26 patients randomly assigned to receive amphotericin B, 1 died and 1 withdrew consent before receiving any medication. These 2 patients were excluded from the efficacy and safety analyses. Another 2 patients did not have histoplasmosis and were excluded from the efficacy analysis. Overall, 73 patients were evaluated for efficacy and 77 patients were evaluated for safety in an intention-to-treat analysis.

The two treatment groups did not differ significantly in any baseline characteristics tested, including clinical features of severe disease (**Table**). The median age of patients was 33 years (range, 16 to 68 years), and approximately 88% of the 73 patients were men. Fifty-two percent were African American, 32% were white, 15% were Hispanic, and 1% were Asian. Baseline blood cultures were positive in 74% of patients.

The overall clinical efficacy of induction therapy differed between groups. Clinical success was achieved in 45 of 51 patients (88% [95% CI, 77% to 96%]) treated with liposomal amphotericin B compared with 14 of 22 patients in the other treatment group (64% [CI, 42% to 83%]) ($P = 0.014$). The difference between groups was 24 percentage points (CI, 1 to 52 percentage points). Twenty-eight of 51 patients (55% [CI, 40% to 69%]) treated with liposomal amphotericin B and 7 of 22 patients (32% [CI, 14% to 55%]) treated with amphotericin B successfully completed therapy before 14 days (difference, 23 percentage points [CI, −2 to 48 percentage points]). The median time to defervescence was 3 days for both therapies (**Figure 2**, *top*). By day 14, however, patients receiving liposomal amphotericin B were less likely to have fever than those receiving amphotericin B (13% vs. 36%; $P = 0.09$ [log-rank test]).

Among the 57 patients receiving itraconazole for consolidation therapy, 89% had a clinical response. Consolidation therapy was successful in 38 of 43 patients (88% [CI, 76% to 96%]) treated with liposomal amphotericin B and 13 of 14 patients (93% [CI, 66% to 99%]) treated with amphotericin B (difference, 5 percentage points [CI, −25 to 35 percentage points]) ($P > 0.2$). There was no significant difference in time to negative cultures ($P > 0.2$). After 2 weeks of therapy, 89% of all patients had negative cultures, regardless of type of treatment. Of the 54 patients with a baseline blood culture positive for *H. capsulatum*, 74% responded to induction therapy and received consolidation therapy. There was no statistically significant difference in negative cultures between the two groups at

Figure 2. **Kaplan–Meier analysis.**



Top. Time to clinical response, as defined by defervescence, for patients with a temperature higher than 37.8 °C 1 day before or at baseline. *P* value for clinical response, defined by defervescence, was 0.09 using the log-rank test. **Bottom.** Survival during induction therapy. *P* value for survival during induction therapy was 0.04 using the log-rank test.

the end of consolidation therapy. *Histoplasma capsulatum* antigen clearance was also similar between the treatment groups. To control for potential investigator bias in outcome responses, data for 42 patients from eight sites were evaluated by using Mantel–Haenszel methods. The odds ratio for clinical response at 2 weeks, comparing liposomal amphotericin B with amphotericin B, was 2.44 (CI, 0.52 to 12.82; $P > 0.2$). Clinical outcomes and mycologic outcomes could not be analyzed at 12 weeks because data for outcomes by regimen were sparse at most of the sites.

Patient survival during induction therapy is shown in the bottom panel of **Figure 2**. One of 53 patients (2%) treated with liposomal amphotericin B died of bacteremia caused by *Staphylococcus aureus* compared with 3 of 24 patients (13%) in the amphotericin B treatment group who died of progression of disseminated histoplasmosis (difference, 11 percentage points [CI, 6 to 37 percentage points]) ($P = 0.04$ [log-rank test]). Of the 57 patients who completed itraconazole consolidation therapy, 5 additional patients died ($P = 0.11$). In the amphotericin B treatment group, one patient died of histoplasmosis at day 17 and another died suddenly, possibly of hypokalemia that occurred at day 38. In the liposomal amphotericin B treatment group, one patient died at day 29 of progression of histoplasmosis, one nonadherent patient died of progression of disseminated histoplasmosis at day 120, and one patient died of opportunistic infections.

Overall, acute infusion-related toxicities occurred in 13 of 53 patients (25%) treated with liposomal amphotericin B and 15 of 24 patients (63%) treated with amphotericin B ($P = 0.002$). Nephrotoxicity occurred in 5 of 53 patients (9%) treated with liposomal amphotericin B and 9 of 24 patients (37%) treated with amphotericin B ($P = 0.003$). Protocol therapy was discontinued because of toxicity in one patient in the liposomal amphotericin B treatment group and two patients in the amphotericin B treatment group ($P = 0.19$).

DISCUSSION

This study demonstrates the clinical efficacy of liposomal amphotericin B compared with amphotericin B for induction treatment of moderate to severe disseminated histoplasmosis in patients with AIDS. The time to defervescence for both treatment groups was rapid, showing a trend toward an earlier response to liposomal amphotericin B ($P = 0.09$). Persistent fever did not seem to be caused by febrile responses to amphotericin B. Mycologic responses to induction therapy were similar for both treatment groups. The rate of blood culture clearance was substantially faster in our study than in a previous study of empirical treatment of mild to moderate disseminated histoplasmosis with itraconazole. In that study, 47% of 30 patients had negative cultures after 14 days of therapy (5; Wheat LJ. Personal communication).

Mortality rates during induction were higher in patients treated with amphotericin B than in those receiving liposomal amphotericin B. Liposomal amphotericin B was better tolerated. Fewer infusion-related side effects and less nephrotoxicity were found in the liposomal amphotericin B treatment group. These results are similar to those of a study of empirical therapy with liposomal amphotericin B and amphotericin B in patients with cancer and neutropenia (17). We performed a sensitivity analysis to account for the possibility that observed outcomes varied among centers. The odds ratio (2.44) of the center-stratified analysis was attenuated when compared with the unadjusted odds ratio (4.29), but it still favored liposomal amphotericin B rather than amphotericin B. Because only 42 of 73 of our patients were included in the stratified analysis, statistically significant differences were difficult to detect.

This randomized, double-blind comparative trial of liposomal amphotericin B for the treatment of disseminated histoplasmosis in patients with AIDS shows the superiority of a lipid formulation of amphotericin B compared with the deoxycholate formulation for invasive mycosis. Despite its higher cost, intravenous liposomal amphotericin B is an attractive alternative for moderate to severe disseminated histoplasmosis in patients with AIDS because of superior efficacy, lower toxicity, and decreased mortality rates.

APPENDIX: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP

Study Investigators and Numbers of Included Patients

Karsten Witt, Gilead Pharmaceuticals, Boulder, CO; Jim Schnieders, Fujisawa Healthcare, Inc., Deerfield, IL; Robert Baker, Community Hospital, Indianapolis, IN (1 patient); David M. Bamberger, MD, University of Missouri–Kansas City, Kansas City, MO (8 patients); John Black, Methodist Hospital, Indianapolis, IN (5 patients); Robert Bradsher, University of Arkansas, Little Rock, AK (2 patients); Patricia Demarais, Cook County Hospital, Chicago, IL (5 patients); Mitchell Goldman, Indiana University School of Medicine, Indianapolis, IN (5 patients); Elliott Goldstein, University of Kansas City Medical Center, Kansas City, MO (1 patient); Richard Greenberg, University of Kentucky, Lexington, KY (1 patient); David Haas and Steve Dummer, Vanderbilt University, Nashville, TN (1 patient); Harold Henderson, University of Mississippi, Jackson, MS (1 patient); Richard Hamill, Houston VA Medical Center, Houston, TX (3 patients); Anna Huang, University of Louisville, Louisville, KY (3 patients); Philip C. Johnson, University of Texas–Houston Medical School, Houston, TX (6 patients); Susan Koletar, Ohio State University, Columbus, OH (5 patients); Dan Lancaster, Methodist Hospital, Memphis, TN (8 patients); David McKinsey, Kansas City, MO (3 patients); W. Peter Pappas, University of Alabama, Birmingham, AL (1 patient); William G. Powderly, Washington University School of Medicine, St. Louis, MO (8 patients); Kenneth Shakan, University of Cincinnati, Cincinnati, OH (1 patient); Patricia K. Sharkey, Audie Murphy VA Hospital, San Antonio, TX (4 patients); John Stansell, University of California, San Francisco, San Francisco, CA (3 patients); and L. Joseph Wheat, Indiana University, Roudebush VA Medical Center, Indianapolis, IN (11 patients).

From the University of Texas–Houston Medical School, Houston, Texas; Indiana University School of Medicine and Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana; University of Alabama at Birmingham, Birmingham, Alabama; Methodist Hospital, Memphis, Tennessee; University of Missouri–Kansas City, Kansas City, and Washington University School of Medicine, St. Louis, Missouri; National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health, Bethesda, Maryland; and Veterans Affairs Medical Center and University of Michigan Medical School, Ann Arbor, Michigan.

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QUALITY GRAND ROUNDS
Series Editors: Robert M. Wachter, MD; Kaveh G. Shojania, MD;
Sanjay Saint, MD, MPH; Amy J. Markowitz, JD; and Mark Smith, MD, MBA

Unexpected Hypoglycemia in a Critically Ill Patient

David W. Bates, MD, MSc*

Administration of the wrong medication is a serious and understudied problem. Because physicians are not directly involved in the drug administration process, they tend to overlook the possibility of adverse drug events and medication errors in their differential diagnoses of patient illnesses or acute deterioration. This article analyzes the case of a patient with iatrogenic hypoglycemia due to administration of the wrong medication: Insulin instead of heparin was used to flush the patient's arterial line. In addition to assessing the results of the institution's "root-cause analysis" of the factors contributing to this particular adverse event and the institution's response, this article reviews the literature on preventing medication errors. Key strategies that might have been helpful in this case include using checklists for common emergency conditions (such as altered level of consciousness) and automated paging for "panic laboratory values," as well as instituting protocols for medication administration. Changing the system of administering medications by bar coding drugs, with checks of the medication, patient, and provider, could have prevented this accident. Finally, organizations need to strive for a "culture of safety" by providing opportunities to discuss errors and adverse events in constructive, supportive environments and by resisting pressure to find a scapegoat.

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"Quality Grand Rounds" is a series of articles and companion conferences designed to explore a range of quality issues and medical errors. Presenting actual cases drawn from institutions around the United States, the articles integrate traditional medical case histories with results of root-cause analyses and, where appropriate, anonymous interviews with the involved patients, physicians, nurses, and risk managers. Cases do not come from the discussants' home institutions.

SUMMARY OF EVENTS

Two weeks following surgery, Ms. Grant (a pseudonym), a 68-year-old nondiabetic woman, became unresponsive and was found to have profound hypoglycemia. The patient had undergone elective cardiac bypass surgery. Complications that developed during the postoperative period were ventilator-acquired pneumonia, a right-hemispheric stroke, clinically significant gastrointestinal bleeding, and acute tubular necrosis that required hemodialysis. Although Ms. Grant remained in the intensive care unit (ICU) because of these complications, her condition stabilized considerably. In fact, her primary physician recalled that on the day of the adverse event, "The patient actually told us that she was comfortable and felt good for the first time. She looked wonderful during rounds."

At approximately 8:15 a.m., Ms. Grant's ICU nurse heard coughing, entered her room, and found her moving her head and extremities in an uncontrolled manner. The nurse administered labetalol because the patient's systolic blood pressure was greater than 200 mm Hg. The ICU team arrived almost immediately, diagnosed a generalized seizure, administered intravenous lorazepam followed by midazolam, and emergently intubated the patient for airway protection. Serum electrolyte and arterial blood gas levels were measured, and computed tomography (CT) was done to rule out intracranial hemorrhage. Approximately 30 minutes after initiation of these diagnostic and therapeutic maneuvers, the laboratory notified the ICU team that the patient's serum glucose level was undetectable.

NOSOCOMIAL HYPOGLYCEMIA

Faced with an abrupt change in their patient's neurologic status, the ICU team considered the possibilities of severe electrolyte disorders, hypoxemia, hypoglycemia, infection, or a severe intracranial event (such as a massive hemorrhagic stroke). In a critically ill patient who is probably receiving many medications, drug effects and medication withdrawal (for example, from benzodiazepines) should also be high on the list of considerations.

Possible causes that quickly respond to treatment should be addressed early. If this patient had been seen in the emergency department, she would have immediately received intravenous thiamine and 50 mL of 50% dextrose in water, even before the results of the laboratory analysis were available. Empirical administration of hypertonic dextrose has been standard practice in emergency assessment of altered level of consciousness. Some controversy surrounds possible adverse effects of this practice (1) because of the deleterious consequences in patients with cerebral ischemia (2). Thus, checking blood glucose levels immediately is ideal, but when this is not possible, rapid administration of hypertonic dextrose is still recommended (3). In hospitalized, nondiabetic patients, on the other hand, empirical management of possible hypoglycemia is not routine, although some authorities recommend it (4). In one study, failure to consider hypoglycemia as a cause of altered level of consciousness was the most frequent error in emergent scenarios (5). Timely diagnosis of hypoglycemia is especially important, because it is usually reversible and the degree of injury depends on how quickly treatment is started. In these situations, checklists can be very useful and should be more widely used.

In the case of Ms. Grant, the diagnosis of profound

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hypoglycemia was confirmed by the undetectable serum glucose level. Although it is not clear when the blood sample was obtained, the extremely abnormal result appears to have reached the team rapidly. Marked laboratory abnormalities for key electrolytes, such as sodium, potassium, and glucose, have been termed *critical laboratory results* and are associated with a high mortality rate (6). A standard approach is for the laboratory to call the patient's unit. Recently, advances in communication technology permit the covering physician to be paged so that the laboratory can report the key abnormality and provide concurrent supporting data for decision making. In a controlled trial at Brigham and Women's Hospital that evaluated a direct-paging approach (7), the intervention group had a median time to therapy that was reduced by 38% ($P = 0.003$) and a trend toward a lower mortality rate (7.4% vs. 13.3% in the control group) ($P = 0.19$).

What are the possible causes of Ms. Grant's hypoglycemia? One review of hypoglycemia (8) organized the diagnostic approaches in terms of the patient's clinical appearance and the clinical setting—patients without apparent illness, ill-appearing patients, and hospitalized patients. In hospitalized patients, major causes of hypoglycemia in nondiabetic patients are drug effects, renal insufficiency, liver failure, sepsis, malnutrition, and shock (9). Adrenal insufficiency can also occasionally present as severe hypoglycemia (10–13). However, the abrupt and profound hypoglycemia in Ms. Grant's case strongly suggested a drug effect.

Medications that can cause hypoglycemia include quinine (14) and its derivatives (14, 15), salicylates, pentamidine (16, 17), and trimethoprim–sulfamethoxazole (18). However, the predominant causes of drug-induced hypoglycemia, even in nondiabetic patients, are the drugs used to treat diabetes (14, 19). The patient's undetectable blood glucose level strongly suggested inadvertent or excessive administration of a hypoglycemic agent.

CHRONOLOGY OF EVENTS

When the patient was being returned to the ICU after the CT scan, the laboratory alerted the ICU to the undetectable serum glucose level. (The CT scan had revealed no evidence of intracranial hemorrhage, mass, or mass effect.) The patient immediately received one ampule of 50% dextrose in water, after which the serum glucose level reached 1.0 mmol/L (18 mg/dL). Administration of a second ampule of 50% dextrose in water produced a serum glucose level of 1.3 mmol/L (24 mg/dL).

At 9:15 a.m., a nearly empty 10-mL vial of regular human insulin (100 U/mL) was found on the medication cart outside the patient's room. This finding, in conjunction with the persistent hypoglycemia despite aggressive glucose replacement, suggested that the patient's sudden deterioration had resulted from inadvertent administration of insulin.

THE WRONG DRUG

Nondiabetic persons can receive diabetic medications as a result of inadvertent ingestion or an error at some stage in the medication ordering, dispensing, or administering processes. Such errors have been well documented for oral hypoglycemic agents (20–28). Similar errors have also been reported for insulin (29). Errors in the administration of intravenous medications are more common than many physicians realize (30). The literature on anesthesia (31, 32) as well as medication errors (33, 34) documents the specific error of administering the wrong intravenous medications to patients.

Additional investigation of Ms. Grant's case should determine whether she had received insulin at any time while in the ICU or whether an order had been written for "sliding-scale" insulin (even if she had not previously received insulin). Other critical information that should be collected is whether other patients in the ICU were receiving insulin and the procedures for handling routine (but high-risk) intravenous medications, such as insulin, in this particular ICU. As with any inquiry into a serious adverse event, issues should be addressed in the context of a "root-cause analysis" (35, 36) in which a team establishes a detailed timeline of the events and activities leading up to the incident. Such teams should be multidisciplinary so that complementary perspectives can help identify the multiple systems defects, environmental problems, and individual stressors that typically contribute to an accident (37).

CHRONOLOGY OF EVENTS, *CONTINUED*

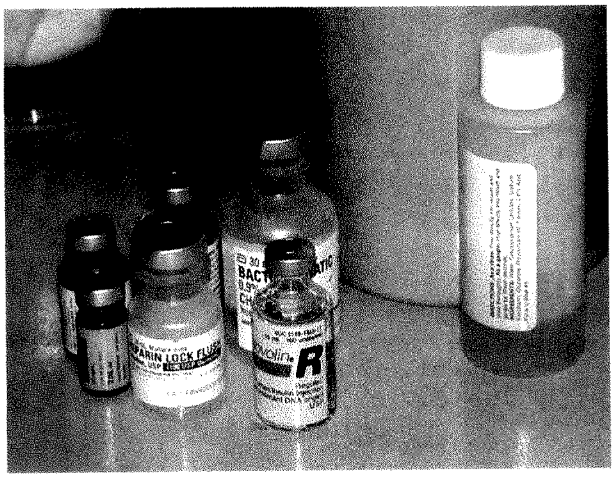
The Table (available at www.annals.org) presents the events leading up to Ms. Grant's abrupt deterioration. The patient had no previous orders for insulin and at the time of the adverse events was the sole patient in the cardiothoracic ICU.

The patient's arterial line had often become occluded, requiring frequent heparin flushes. The institution conducted a root-cause analysis, reconstructing the patient's care leading up to the event. Strong circumstantial evidence suggested that the intended 1- to 2-mL heparin flush at 6:45 a.m. was insulin and not heparin; thus, the patient received 100 to 200 U of regular insulin on at least one occasion.

A SYSTEMS APPROACH TO MEDICATION ERRORS

In general, systems are most effective when they decrease the likelihood of errors, identify those that do occur, and respond rapidly to serious deviations. In this case, the deficiencies in the system that made an error more likely included the failure to store medications properly, the lack of checks in medication administration, and the less-than-optimal response to the patient's deterioration. The primary error appears to have occurred at 6:45 a.m., when insulin was used to flush the arterial line, although no change in the patient's condition was detected until

Figure. **Heparin and insulin vials as they appeared on the patient's bedside cart in the intensive care unit.**



8:15 a.m. The time sequence (**Table**, available at www.annals.org) and additional information (**Appendix**, available at www.annals.org) help reconstruct the events. Both heparin flush solution and insulin were taken from multidose vials that were on the top of the cart at the time of the error. Both types of vials hold 10 mL of solution, and the vials look somewhat similar (**Figure**). Although the insulin should have been kept in the refrigerator, it was often left on the top of the cart after being taken out of the refrigerator, a practice that psychologist James Reason (37) would term an *unsafe act*—something that violates a policy or procedure but is often done to save time.

THE EPIDEMIOLOGY OF MEDICATION ERRORS AND ADVERSE DRUG EVENTS

Medication errors occur much more frequently than do adverse drug events, although most have little potential for harm (34, 38). Adverse drug events occur when a drug causes injury; if an adverse drug event is associated with an error, it is considered preventable. Medication errors with potential for harm that do not cause injury are considered potential adverse drug events. Thus, the case described here represents a preventable adverse drug event. One study (34) found approximately 100 medication errors for every preventable adverse drug event and seven potential adverse drug events (or near-misses) for every preventable adverse drug event. In another large study (38), the rate of occurrence of adverse drug events was 6.5 per 100 admissions, of which 28% were preventable. In that study, the stage at which serious medication errors (potential adverse drug events and preventable adverse drug events) occurred was broken down as follows: 49% at the ordering stage, 26% at the administration stage, 14% at the dispensing stage, and 11% at the transcription stage. Errors were much more likely to be intercepted if they occurred at an early stage of the medication use process.

"Wrong drug" or "wrong patient" errors represented 4% of all medication errors in hospitalized medical patients in a study that used various approaches to review records of such errors (34). The most sensitive approach for detecting medication administration errors is probably direct observation (39). Barker and Allan (33) developed an approach in which a trained observer watches a health care professional, notes what he or she does when administering drugs, and watches the patient receive the medication. This approach is now widely used in health care organizations, most notably in long-term care facilities; federal inspectors use the approach in the facility licensing process. In acute care settings, the Barker and Allan technique reliably identifies about one error per patient per day (33). In a large recent study using this approach, only about 1% of detected medication errors were in the "wrong drug" category (40).

Of the medication errors that result in serious injury, however, the proportion of "wrong drug" errors (frequently involving insulin) appears to be much higher than the approximately 1% reported by Flynn and colleagues (40). In a national survey, Cohen and colleagues (29) found that 11% of serious medication errors resulted from insulin misadministration. One common error is misreading the abbreviation "U" as "0" such that "10 U" is read as "100." Another recurring type of error involving insulin is drug substitution (29), as occurred in this case. This error has been reported several times to national error reporting systems (41), which play an extremely important role in aggregating rare, serious errors. In the chapter on high-alert medications in Cohen's seminal book on medication errors (42), the first bullet for insulin reads:

> Intravenous insulin is lethal if it is given in substantially excessive amounts or in place of other medications. Insulin and heparin are often mistaken for one another because both are administered in units and both may be stored in proximity to each other.

THE ROLE OF INDIVIDUAL ERRORS IN CAUSING THIS ADVERSE EVENT

This case represents a common error—almost certainly a "slip." A "slip" is one of the two primary classes of errors. Slips occur during low-level, semiautomatic everyday functions. They are distinct from the other primary class of error, "mistakes," which involve higher cognitive function and occur in new or nonstereotypical situations.

In this case, the nurse clearly intended to give heparin, but because both types of vials were on the top of the cart, he "slipped" and inadvertently selected the wrong one. Poor systems design increases the likelihood of slips resulting in catastrophic harm. A classic medical example is giving a gas other than oxygen to a patient receiving anesthesia, often with disastrous consequences (43). This error has been largely "engineered out" of anesthesia, using what is termed a *forcing function*. Anesthesia machines are now built with a unique oxygen yoke that prevents attachment of any other type of gas.

In this case, which is similar to many preventable adverse events in medicine, an individual made a clear-cut error. The nurse should have checked the vial to ensure that it contained heparin before giving the medication. However, such slips are inevitable, especially given increasing time pressures and workloads: Humans are not "perfectible" (44). If one person exhibits a pattern of poor performance, appropriate action should be taken. However, most errors are made by competent providers. In a report from the Adverse Drug Event Prevention Study Group that evaluated more than 250 serious errors (45), no one person showed a recurring pattern of error.

THE ROLE OF SYSTEMS IN THIS ADVERSE EVENT

The systems and processes of care clearly played a major role in this adverse drug event. In the ICU, it was routine practice to have heparin and insulin accessible at the same time and to use multidose vials. In addition, there was no system of second checks (by another person) before high-risk drugs were administered. Also, the institution did not have a system of bar code checking. In responding to the adverse event, it is not clear whether physicians had a protocol for responding to hypoglycemia. The patient probably should have received glucose earlier and should have been treated more aggressively, because the dangers of overadministration of glucose are lower than the risk from prolonged hypoglycemia.

PREVENTION STRATEGIES

A variety of approaches may have prevented this adverse event, although it is important to note that the strength of evidence for safety practices overall varies substantially and is generally weak (46). Multidose vials of insulin, in particular, should not be kept on top of medication carts and probably should not be used at all. Insulin should be drawn up at one site in the nursing unit or, even better, prepared in the pharmacy. After insulin is drawn up, a second provider should independently check the original order. Bar coding, if strictly adhered to, could also have prevented this type of drug-substitution error (47).

It is important to note that applying the criteria of evidence-based medicine to safety practices has been challenging for a variety of reasons (46). Because adverse events occur rarely, trials are expensive; because many practices (for example, sponge counts) have become accepted, it would be difficult to subject them to trials; and because many practices are systems- and culture-oriented, they are not especially amenable to randomized trials. It is not clear whether trials are appropriate for many safety-related issues, especially given that other industries, such as aviation, have substantially improved safety without randomized trials (48).

CHRONOLOGY OF EVENTS, CONTINUED

The physicians caring for the patient and the medical center's physician-in-chief met with the family within hours after the adverse event. The error and the immediate actions were explained, and the prognosis and need for supportive treatment and watchful waiting were discussed. The physicians and staff expressed profound regret and sorrow for the medical error. The family was understandably upset but appreciated the acknowledgment that a mistake had occurred.

The patient remained in a coma for 7 weeks. At that point, after discussion with the family, life support was discontinued and the patient died.

THE INSTITUTIONAL RESPONSE

The hospital implemented the following procedures and policies:

1. Insulin was added to the automated dispensing device.
2. All staff who obtain medications from ward stock were instructed to keep medications secured in authorized places.
3. All nurses were reminded to keep medication carts locked when not attended.
4. Use of multidose vials of insulin and of heparin was prohibited.
5. Use of normal saline flushes to restore patency to arterial lines (instead of heparin flushes) was required.
6. An interdisciplinary team, composed of a staff pharmacist, pharmacy manager for inpatient services, staff nurse, clinical coordinator, physician, and clinical risk manager, was established to examine how to expedite the delivery of medications to patients while maintaining optimum medication practices.

COMMENTS ON THE INSTITUTIONAL RESPONSE

How institutions respond to adverse events is vitally important if an organization is to build a culture of safety. With respect to patients and their families, a consensus has emerged that the most appropriate and ethical course is to immediately disclose an adverse event. Doing so is now required by new regulations from the Joint Commission on Accreditation of Healthcare Organizations (49). A report from the Department of Veterans Affairs argued persuasively for a full-disclosure policy and described one of its medical centers that has had moderate liability payments since implementing this approach in 1987 (50).

The fear, of course, is that increased reporting, especially coupled with disclosure, could lead to skyrocketing malpractice litigation rates in the United States. A no-fault compensation approach for medical injuries (51) may alleviate this problem, but the obstacles are substantial. The current system strongly pressures providers to hide accidents rather than to bring them forward as a means to fuel quality improvement. Furthermore, persons who report adverse events may be punished (52). The tone set by administrators is crucial. Although remedial action should be taken, leadership must resist strong pressures to use individual workers as scapegoats, even when a serious error is found. Organizations that yield to these pressures will find it exceptionally difficult to develop a safety-oriented culture.

When given the opportunity to respond anonymously, individual providers recognize that error is a serious issue, but they harbor many counterproductive feelings that hinder development of a culture of safety. In an anonymous survey of internal medicine house officers regarding their most serious mistakes, Wu and colleagues (53) found serious adverse outcomes in 90% of the cases, including death in 31%. Only 24% of the responsible housestaff told the patients or families, and just 54% had even discussed the mistake with their attending physicians. House officers who accepted responsibility for and discussed the mistake made constructive changes more often. Those who attributed the mistake to job overload were less likely to respond positively. They reported defensive changes more often if they felt the institution was judgmental.

Providers involved in accidents feel guilty, tend to be overly self-critical, and need support (54, 55). Organizations should provide opportunities to discuss errors and adverse events in constructive, supportive environments. In general, hospitals have made a low overall investment in safety. One welcome response to the U.S. Institute of Medicine report on error (56) has been to increase this investment. Hospitals are increasingly providing support for a safety officer (often a physician) who, with staff and a budget, is charged with improving the safety of the organization. Historically, most of this function has been carried out by the risk management department, which in many organizations has focused primarily on dealing with potential lawsuits—a necessary role, but one that has been more reactive than proactive. This new and vital patient safety role should include close teaming of health care providers with risk management personnel. Safety officers should review the myriad suggestions being made by various groups (such as the Institute for Safe Medication Practices), evaluate their organization's current practices, and encourage implementation of those procedures and policies that make sense. Only with more resources and support for safety will we develop a health care system that learns from the errors and accidents of others so that each site does not suffer its own disaster before procedures are improved.

Approaching patient safety problems is analogous to containing water in a sieve. In choosing how to apply resources to improve safety, institutions must decide whether to prioritize fixing "individual leaks" or overhauling the system (finding a container with fewer holes). A combination of approaches may often be appropriate. An evidence-based approach to prioritization of systems changes, especially their impact and costs, has begun but could be greatly expanded (46).

The approaches selected by the hospital in this case for preventing medication administration errors are reasonable, although some are stronger than others. Elimination of multidose insulin and heparin vials will probably be very effective; the educational measures will be less so (57). Moving insulin to the automated dispensing device is also desirable, although it may be more effective to prepare insulin in the pharmacy, at least for routine daily doses. Switching from heparin to saline flushes is a positive step that is supported by the available evidence (58). Developing a multidisciplinary team to evaluate the medication process on an ongoing basis is also a key step. With the exception of the elimination of heparin flushes, these changes amount to patching leaks rather than overhauling the system, which would involve fundamental redesign of the medication administration process and incorporating key systems changes (such as bar coding technology) (59).

CONCLUSIONS

As is generally the situation when preventable adverse events are assessed, several opportunities for improvement could be found. In Ms. Grant's case, although the nurse made an error, he was "set up" to do so by poorly designed systems. The organization in this instance made appropriate short-term changes to its drug administration system, but its future course in this domain is unclear. In particular, bar coding would probably have prevented this accident. In addition, the team's response to the patient's altered level of consciousness could have been more effective and use of a checklist to prompt a systematic approach to altered mentation might have been helpful. Finally, all organizations need better ways to prioritize and implement key systems changes before accidents occur.

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The Table, Appendix, and excerpts of the question-and-answer session are available at www.annals.org.

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Reforming Care for Persons Near the End of Life: The Promise of Quality Improvement

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Most people in developed countries will live with a serious, eventually fatal, chronic condition for months or years before dying; yet, the delivery of health care services has only just recently begun adapting to this reality. Quality improvement methods have been effective in helping clinical services to make substantial changes quickly.

Quality improvement requires stating an aim, measuring success, and testing possible improvements. The testing of changes requires a clinical team to Plan, Do, Study, and Act on new insights (the "PDSA cycle"). Repeated PDSA cycles generate deep understanding of complex systems and make sustainable improvements rapidly.

This paper discusses a composite case study in a nursing home setting, which builds on experience with multisite collaborative efforts and introduces quality improvement methods in the context of end-of-life care.

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Dr. Evan Thomas, a hospitalist, was called to the emergency department to admit an 84-year-old woman from a nearby nursing facility for hospitalization. He started to perform a routine work-up for fever and administered intravenous antibiotics. The patient had no family, and her court-appointed guardian was unavailable. After experiencing many complications, the patient developed decubiti from fighting restraints and was "barely hanging on." Dr. Thomas called the patient's nursing home facility to find a nurse who knew her, but none was available. The patient had a feeding tube and a resuscitation attempt before she died.

Thereafter, Dr. Thomas was increasingly troubled by his patients from nursing home facilities. Few of these patients had any living family, and almost none had plans about issues like resuscitation. These patients comprised one third of Dr. Thomas's caseload, but he was not sure that the care he provided served their interests.

RECOGNIZING A PROBLEM

Dr. Thomas has taken the first two crucial steps toward improvement. First, he is developing the will to make changes because he sees that his care falls short, at least in managing symptoms and planning for advance care. Second, he recognizes that this care pattern affects many patients. Accepting the status quo is what blocks most opportunities for improvement, and ferreting out a particular person responsible for one error rarely yields important improvements. Substantial gains result from correcting a behavior pattern that affects dozens of patients.

STARTING A PROCESS

Dr. Thomas sought better options in professional literature and in programs to serve severely demented adults. He talked with the directors of nursing and social workers at two good local nursing home facilities as well as experienced geriatricians. He listed possible improvements, most of which required agreement about practices and plans among the nursing home facilities, the emergency medical system, and the hospital. He decided to bring together a dozen concerned persons to see what might be done.

Dr. Thomas has learned much about the problem, has assembled a team that cares about it, and has developed a list of changes to attempt. This process could lead to responsible and effective implementation of changes. To facilitate improvement, someone has to identify shortcomings in how care is delivered, examine the impact of those shortcomings, consider alternatives, and initiate action. Generating quality clinical environments depends on recognition by his hospital's chief executive officer and by his other colleagues that improvement is important and deserves their support, despite the disruption this may cause.

GETTING STARTED

Dr. Thomas's group gathered. They told stories of shared patients and commented on what worked well. They also discussed frustrations and identified gaps in continuity and services. They settled on two immediate actions: 1) to get all health professionals in the area to agree on one way to communicate patients' decisions to forgo resuscitation and 2) to make plans about advance care planning at each quarterly review at one nursing home. Although they hoped eventually to involve a wide array of physicians and organizations, the group started small, working with those who were easily persuaded to make improvements.

The director of nursing at a nursing home facility offered to arrange meetings of the group and keep everyone informed by e-mail. Three people agreed to find or develop a form for communicating decisions about cardiopulmonary resuscitation, and the entire group agreed to meet again in a month.

This story is a composite drawn from broad experiences, but most stories of success start this way, with the "frontline" providers committing to real change. This group has bypassed the common diversions of spending too much time gathering information and making plans or

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putting all their efforts into standard continuing education projects. Instead, they are trying two changes on a small scale. They will have evidence of how those attempts are working in a month, at which time they can make adjustments, can continue that work, and start new projects. They will use the *PDSA cycle*, a routine of Planning a change, Doing it, Studying its effects, and Acting on the insights gained. On the basis of what they learn, the group will spread the useful changes more widely throughout their institutions.

MAKING CHANGE HAPPEN

While seeking a common tool for communicating resuscitation decisions, the team encountered Oregon's Physician Orders for Life-Sustaining Treatment (POLST) (1). They adapted the POLST, including negotiating agreements from legal authorities, community leaders, and health care organizations. That work got a boost when the local newspaper published a series of articles on end-of-life care that highlighted this project. However, a local religious leader wrote a strongly worded letter to the editor, cautioning that the poor could be pressured to forgo treatment just to save money. After several conversations, the letter writer agreed to join the group to watch over the process.

The coalition realized early on that it would need to measure results. The rate of documented do-not-resuscitate orders in the minimum data set (standard data collection for nursing facilities) in five local nursing facilities that adopted the POLST went from 28% to 52% over 6 months, and the rate of transfer of do-not-resuscitate orders to the hospital went from 2 in 12 during the 3 months before the project to 6 in 8 during a 3-month period that started 6 months later.

The team at the nursing home that was attempting to institute routine consideration of advance care planning had its problems, too. First, they found that many patients had pre-existing written advance directives that were not included in the facility's records. Second, clinicians did not routinely ask patients or their families to make decisions in advance, in part because they were uncomfortable having these discussions. A chaplain at a nearby hospital was asked to provide training for the entire interdisciplinary team of nursing facility representatives. Although an audit of medical records initiated by the project found only 12% of the patients having advance care plans documented, a repeat audit 1 year later found 34%.

The pace of change varies: Some issues move along quickly, while others require struggle. The challenges that arise can be instructive. For example, the hostile letter to the editor of the newspaper gave voice to a realistic concern, and including that perspective in the work was valuable. Likewise, the chaplain's training of the staff was more effective because it arose from the experience of thwarted improvement attempts. Success requires a rapid and visible pace of change, along with leadership support. Most teams can sustain a few simultaneous improvement activities, and the most effective teams become infectious, passing along their enthusiasm and the essentials of their approach. However, although the quality improvement method structures the work and improves the likelihood that reforms can be implemented and sustained, this work is still very difficult, and even the most successful quality improvement projects will encounter barriers and difficulties.

THE TRACK RECORD OF REFORM IN END-OF-LIFE CARE

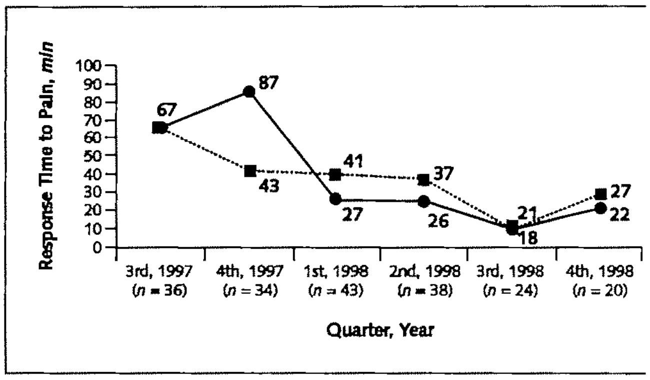
Over the past 30 years, end-of-life care has gradually improved, at least by some measures. The rate of per-capita opioid use has increased by more than 10-fold (2). In years past, physicians often did not tell patients of a diagnosis of cancer, nor did they provide patients with effective pain relief. Now, however, virtually all such patients receive at least a diagnosis and basic pain treatment. Hospice has shown that better care is possible in targeted, dedicated, and comprehensive care systems (3).

Nevertheless, most efforts to improve care delivery have been less clearly effective. The Study to Understand Prognoses and Preferences for Risks and Outcomes of Treatments (SUPPORT) (4) tried to enable thousands of very sick patients to shape decision making but failed to change behaviors or outcomes. Research has not found improvements in patient care on the basis of standard advance directives (5, 6); however, a recent report (7) found that the level of anxiety among family members was reduced by planning for complications and death. The strongest determinant of locus of care at the time of death across regions is the availability and use of hospital beds (8), not the patient characteristics that ethical standards advocate.

Researchers and political leaders offer basic research as a method of reform, and improved therapeutic options have contributed substantially to improved care. Still, the care system routinely fails to use proven methods. Most people who have serious pain do not need advanced methods; they just need the morphine and counseling that have been available for centuries. Most patients with congestive heart failure do not receive the best drugs, and most do not know how to manage their illness (9). Most patients with asthma do not even know how to use their inhalers (10, 11). Research has created opportunities that cannot be fully implemented without a focused system to deliver better care. That gap is what makes it important to improve care through practical, common-sense efforts to improve care, like those of Dr. Thomas.

In July 1997, the Institute for Healthcare Improvement and the Center to Improve Care of the Dying launched a yearlong collaboration among teams from four dozen provider organizations across the United States and Canada (12). With the guidance of experts and sound methods for improvement, most made substantial improvements for their patients. One hospital-based team found, much to their chagrin, that the average patient with cancer waited 3 hours for pain medication. Within just a

Figure 1. **Response time to pain by quarter-years and split by time from assessment to orders and time from orders to administration.**



Shown are the average time elapsed from assessment to orders (*solid line, circles*) and the average time elapsed from orders to treatment (*dotted line, squares*). Used with permission from Jean Brontoli, St. Mary's Health Center, St. Louis, Missouri.

few months, the team was able to decrease the average response time to less than 1 hour by working to improve and standardize assessment and treatment (**Figure** 1). Another team found that patients received medications more quickly when an on-the-scene nurse was authorized to adjust dosages within an agreed-upon range. Many found that pain was simply being ignored, and they required measuring pain as "the fifth vital sign." One team virtually abolished severe and persistent dyspnea in patients receiving hospice care by prioritizing responses, having a physician-endorsed treatment protocol, having a back-up physician if the attending physician did not respond or the problem persisted, and having appropriate drugs already present where the patient lived (ready to administer with a telephone call) (**Figure** 2).

Virtually every team that worked on family support made improvements that mattered. Some initiated bereavement support. Some tackled fixing issues that made families angry. For example, many hospitals were sending the bill for the final hospital stay to the deceased patient, and families viewed this as evidence that no one cared. However, by changing the computer address to "The estate of [the deceased patient]," the problem was fixed. Other teams ensured follow-up with family after a death, and two teams provided beepers to family caregivers so that they could be absent from the patient (for example, to take a nap or run errands). Another team provided a place to shower and nap while a loved one was in the hospital.

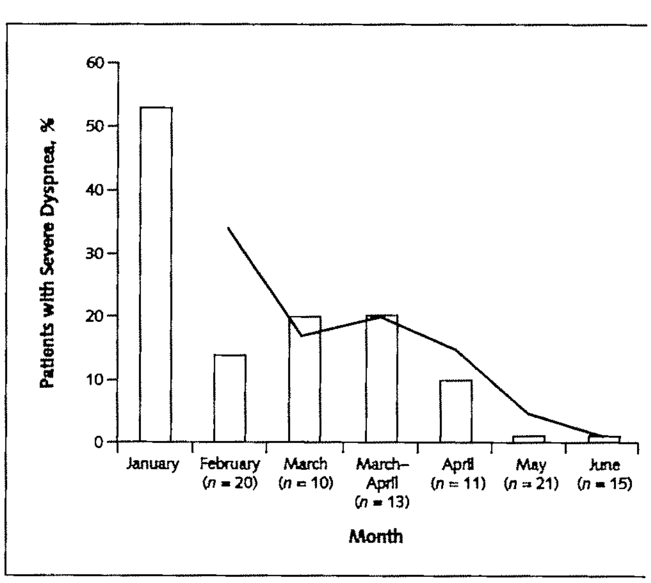
These teams not only improved their programs but also learned several generalizable insights. For example, teams learned to identify patients to target for special services by using the question: "Which patients are sick enough that it would not be surprising if they died in the next 6 months?" It does not matter whether one asks about a few months or a year—either way, the question encourages physicians to recognize that the patient is very sick, although some who are "sick enough to die" will actually live a long time. By using this approach, many more patients were identified far enough ahead of death for hospice and other end-of-life services to make a difference in their lives.

A few years ago, health care providers in La Crosse, Wisconsin, started a community-wide effort to improve advance care planning (13). They instructed elderly persons in senior centers, patients coming to office visits, and ordinary citizens through a mass media campaign. As a result, 85% of more than 500 decedents in La Crosse had an advance directive at the time of their death, and the directive had been written, on average, more than a year before the patient died. Ninety-eight percent of dying people had deliberately forgone some treatment, and virtually all of the advance directives were followed. How did the health care providers accomplish this? They supported shared goals through an array of trials of interventions, assessments, and broader dissemination and implementation of successful efforts.

RAPID-CYCLE QUALITY IMPROVEMENT

Associates in Process Improvement and others have designed an effective and useful method of rapidly initiating changes (14, 15). The PDSA model for improvement starts with teams asking themselves three fundamental questions: 1) What are we trying to accomplish? (aim); 2) How will we know whether a change is an improvement? (measure); and 3) What changes can we make? (changes).

Figure 2. **Rate of dyspnea that persisted for more than one hospice care shift.**



Shown are the quarter-year rates (*bars*) and 2-month moving average (*solid line*) of severe dyspnea not relieved by end of shift. Used with permission from Joan Teno, MD, Brown University, Providence, Rhode Island.

What Are We Trying To Accomplish?

The answer to this question is the foundation for the team's goal. Compelling aims are usually brief, measurable, and important to patients and families. The aim should be documented and circulated for comment to those with a stake in the outcome of the project.

How Will We Know Whether a Change Is an Improvement?

Measurement is an important part of the improvement process; it allows teams to quantify the impact of changes and determine whether they work. Measurement should answer specific questions—for example, "Did the rate of pain decrease after instituting a protocol?" "Did written information, reminders, and the tools to manage exacerbations at home lead to lower rates of visits to the emergency department?"

What Changes Can We Make?

Patients, families, providers, and managers all have ideas about "what would work better." A review of the literature and of the experiences of others often finds changes that are well tested but not extensively used in clinical practice. With complementary answers to these three questions, teams can then test the most appealing changes by using the PDSA cycle.

THE PLAN–DO–STUDY–ACT CYCLE

The model for improvement is based on a trial-and-learning approach. The PDSA cycle provides the framework for effecting change by planning the change, trying it, observing the consequences, and acting on what is learned from those consequences. All four steps are important. All too often, a change is tried but not evaluated, and nothing useful is learned.

Even an ambitious and innovative change can be tested first on a small scale—for example, with one or two physicians, with the next five patients, over the next 3 days, or one component at a time. The change that is eventually implemented could be a substantial departure from current practice; however, implementing small increments repeatedly can overcome some of the reasons for inactivity, such as fear of risks, lack of resources, and a lack of confidence that the change will work.

Measurement of effect is critical to learning from tests. The most convincing measures are documented in a time series—for example, percentage of clinic patients *per month* who have had an advanced care planning discussion or the average response time for pain relief on the oncology unit *each week*. The temporal relationship between changes made and the results builds evidence that the changes led to improvement. Sometimes measuring before and after or intervention and control is sufficient. If such a measurement strategy is used, additional qualitative assessments of the effects of the changes help innovators to learn from each cycle and to refine the changes. The team should aim to have just enough evidence to confidently assess whether changes resulted in improvements or problems.

Testing multiple changes among dozens of teams during collaborative quality improvement provides an opportunity to quickly learn complex system behaviors. Those insights can provide leverage to other organizations interested in improving care (16).

QUALITY IMPROVEMENT IN RELATION TO CONVENTIONAL RESEARCH

In science today, carefully designed randomized experiments and tests of hypotheses are often the only trusted avenues to gaining knowledge. Other formal research methods, such as case–control or cohort studies, are also trusted to provide insights. However, the art of medical care involves a continuing, individualized search in which the physician tries to match incomplete scientific knowledge of disease and treatment with incomplete knowledge about particular patients and local care systems. Physicians do not often know the way but find it step by step, inductively learning from experience caring for real patients. Often, in discerning how to care for a specific patient population, steady investigation with small-scale tests of change is more useful than are randomized, controlled trials. The alternative to using a sequence of PDSA cycles and data plotted over time is not usually a randomized trial followed by widespread implementation; instead, it is usually continuing present practices or making changes without evidence or evaluation.

When linked to important aims and thoughtful reflection, PDSA cycles are powerful tools for learning in complex, improvement-oriented systems. Practice patterns vary widely in every medical discipline across the United States (17). For example, U.S. rates of breast-conserving surgery for breast cancer vary more than 30-fold (18). Similarly, most elderly persons with a myocardial infarction do not receive β-blocker therapy after the acute management stage of care (19). Rates of cesarean section range from 8% to more than 40% among hospital service areas (20). Practice patterns vary so widely that not all practitioners can be right.

When the relative benefit of a particular drug or operation is uncertain, a randomized, controlled trial is the study design that regularly yields a confident comparison. However, clinical trials will not help to develop an improved patient flow or to adapt a specific treatment or flowchart for use in a local setting. Indeed, most learning and improvement in real-world settings come neither from erratic trial and error nor from randomized experiments but from "PDSA" science (14).

In the late 1980s and early 1990s , the Northern New England Cardiovascular Disease Study Group (21) assessed variations in outcomes and processes of care among participating heart surgery centers. Round-robin visiting among surgical teams and analyses from a voluntary database on surgical outcomes and complications allowed clinical groups to identify promising changes in numerous components of cardiovascular surgery, including patient selection, preoperative preparation, bypass pump management, hemostasis, and anesthesia. These observations led to numerous local PDSA cycles, the results of which were reported back to the group. The overall result was a 24% reduction in the number of deaths from coronary artery bypass graft surgery throughout the region. It is hard to imagine how formal, large-scale, randomized trials could have been implemented and achieved this dramatic change.

Of course, it might well be appropriate to test a drug or device in a randomized, controlled trial in the same patients with whom teams are working to find ways to diminish waiting times or to smooth transitions from hospital to home. In short, the method that is implemented needs to be appropriate to the issue being addressed.

LESSONS TO LEARN

Dr. Thomas and the group did many things that other innovators could take to heart. For example, Dr. Thomas took responsibility and got things started, and he got the right people involved, including senior leaders. The group took on problems that affected patients and for which they were responsible. They also used existing knowledge as the basis for their changes, adapted existing tools and skills from other areas to their own needs, measured results over time, and started small (with just one nursing facility) for the tougher problems and built knowledge about the changes sequentially. Finally, their successes catalyzed larger changes and an attitude of welcoming innovation and improvement.

CONCLUSION

The time is right for innovation and change in end-of-life care, guided by measurement and catalyzed by effective networking among innovators. Rapid-cycle quality improvement creates momentum for change that reformers can respect and use and has been widely effective in improving the care of seriously ill patients (12, 16). The health care system needs multifaceted change that aims for consistent, high-value, high-quality care at the end of life. Each of us must ask what shortcomings in end-of-life care affect the places where we practice, how they can be addressed, and how improvements can be accomplished. To prepare to meet the needs of our aging population, we must harness our resources and commit to these efforts now.

APPENDIX: MEMBERS OF THE ACP–ASIM END-OF-LIFE CARE CONSENSUS PANEL

Bernard Lo, MD, (*Chair*), University of California (San Francisco, CA); Janet Abrahm, MD, University of Pennsylvania (Philadelphia, PA); Susan Block, MD, Dana Farber Cancer Institute (Boston, MA); William Breitbart, MD, Memorial Sloan-Kettering Cancer Center (New York, NY); Ira Byock, MD, Palliative Care Services (Missoula, MT); Kathy Faber-Langendoen, MD, State University of New York Health Science Center (Syracuse, NY); Lloyd W. Kitchens Jr., MD, Texas Oncology (Dallas, TX); Paul Lanken, MD, University of Pennsylvania (Philadelphia, PA); Joanne Lynn, MD, RAND Center to Improve Care of the Dying (Arlington, VA); Diane Meier, MD, Mt. Sinai School of Medicine (New York, NY); Timothy E. Quill, MD, The Genesee Hospital (Rochester, NY); George Thibault, MD, Partners Healthcare System (Boston, MA); James Tulsky, MD, Veterans Affairs Medical Center (Durham, NC). Primary Staff to the Panel: Lois Snyder, JD (*Project Director*), ACP–ASIM (Philadelphia, PA), and Jason Karlawish, MD (*Clinical Staff*), University of Pennsylvania (Philadelphia, PA).

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EDITORIAL

Fever, Neutropenia, and the Second Law of Thermodynamics

The management of the patient with cancer who has chemotherapy-induced neutropenia and fever has changed markedly over the past four decades. Empirical antimicrobial therapy is now the standard of care for any patient with cancer and neutropenia who has unexplained fever, rigors, or subtler signs of sepsis (for example, unexplained tachypnea, volume requirement, or acidosis). Although different organisms have been found in these patients over time (Enterobacteriaceae and *Pseudomonas aeruginosa* through the 1980s, and now mostly gram-positive organisms), empirical therapy has been validated by several well-designed comparative trials, including studies conducted by the European Organisation for Research and Treatment of Cancer, the National Institutes of Health, and numerous academic medical centers (1). The study by Peacock and colleagues in this issue (2) adds significantly to our understanding of the effect of this approach in desperately ill patients with cancer.

What have we learned from this effort? First, temporal factors are important. Whereas gram-positive bloodstream infections must be treated, immediate initiation of vancomycin therapy is not essential unless the patient is already in extremis. Thus, gram-positive therapy can be delayed until an invasive gram-positive infection is identified on culture or by careful examination of the patient in question (3). Gram-negative coverage, in contrast, must begin immediately because the patient will otherwise be at risk for gram-negative sepsis, which can progress rapidly in persons with neutropenia.

Second, there is a logical sequence in which antimicrobial agents ought to be prescribed: Broad-spectrum anti–gram-negative therapy should be started immediately, and antifungal therapy should be used 72 to 96 hours later if the patient has not responded. Vancomycin should be added to the regimen if culture or physical examination reveals a gram-positive infection or if the empirical anti–gram-negative therapy has limited coverage of viridans streptococci (3, 4). Antianaerobic antimicrobial therapy should be used only when suspicion for an anaerobic infection is high, and it is rarely justified for use as empirical therapy. This strategy of antimicrobial deployment has greatly improved the survival of patients undergoing chemotherapy or bone marrow transplantation. However, continued close observation of the patient is an important and necessary part of this strategy. If the patient's condition deteriorates, then immediate administration of the full antimicrobial program is indicated.

Third, patients with cancer and neutropenia can develop a fever for various reasons, including noninfectious causes (for example, drug allergies; transfusion reactions; drug toxicities; or, in patients undergoing bone marrow transplantation, immunologic response to a histologically incompatible transplant) and infectious causes (for example, bloodstream infections related to infected vascular access devices; infections related to damaged mucocutaneous surfaces that permit the invasion of gut and skin flora because barrier function has been compromised; and, finally, infection from contaminated air, contaminated water, or contact with other persons who have contagious infection). Indeed, the risk for infection in these patients has been shown to involve an interaction of three factors: the patient's net state of immunosuppression, environmental exposures, and possible anatomic abnormalities that are susceptible to microbial invasion.

Fourth, use of empirical therapy for febrile neutropenia is justified because of the insensitivity of currently used culture techniques and the limited time available to gain control of infections, particularly those that are gram-negative. Thus, immediate initiation of anti–gram-negative therapy is required. It is to be hoped that through the development and use of improved diagnostic methods (for example, non–culture-based diagnostic approaches, such as polymerase chain reaction), empirical therapy guided by algorithms will be replaced by preemptive therapy guided by laboratory markers that correlate with real, albeit early, infection.

Although prompt initiation of empirical therapy is the best currently available treatment for this condition, considerable controversy remains regarding the details of this approach. First, the absolute neutrophil count at which therapy should be initiated for maximal benefit and minimal cost and toxicity (<1, <0.5, or $<0.1 \times 10^9$ cells/L) is unclear (5). Our approach is to accept a count below 1×10^9 cells/L, provided that the patient's neutrophil count is expected to decrease to below 0.5×10^9 cells/L as a result of chemotherapy over the next few days. Indeed, an important end point not delineated in the report by Peacock and colleagues is the success of each regimen during the time of most profound neutropenia.

The second controversial issue involves the appropriate end points for judging success or failure. This study and other recently reported studies have used a demanding composite end point; specifically, success was defined as defervescence or the lack of need for additional antimicrobial agents (6). However, this patient population can become febrile for a plethora of possible reasons, many of which are not amenable to antimicrobial therapy. Moreover, 62.5% of the patients in the study by Peacock and colleagues had vancomycin added empirically to their antimicrobial regimen. Because the ultimate aim is not to eradicate fever or to avoid use of additional antimicrobial agents but to keep the patient alive during a period of maximal vulnerability, it is not surprising that fewer than one third of the study patients in both treatment groups achieved the composite end point. Thus, other end points need to be developed and validated. Any study in which fewer than one third of the patients achieve the desired end point raises the question of what is truly happening in most of the patients.

The choice of antibiotic regimens for empirical therapy of the patient with fever and neutropenia is likewise in some dispute. Most clinicians agree that a broadly active program to treat Enterobacteriaceae and *P. aeruginosa* infections is the first step, and such a program can be achieved in several ways. For example, clinicians could prescribe a single broad-spectrum drug, such as a carbapenem, or an advanced-spectrum β-lactam, such as ceftazidime, or the drug combination piperacillin–tazobactam. Potentially synergistic therapy with a β-lactam–aminoglycoside combination (as in one group of the current study) could also be considered. Other drug combinations could be prescribed, such as piperacillin–ciprofloxacin, which was administered to one of the treatment groups in the current study. For practical purposes, as long as a prolonged bactericidal effect is achieved, the results appear to differ little, with the possible exception of infection due to *P. aeruginosa*. For this scenario, many experts prefer an antipseudomonal β-lactam in combination with an aminoglycoside. Although the study by Peacock and colleagues has not identified the optimal therapy for infection with *Pseudomonas* species, it has established the overall effectiveness of piperacillin–ciprofloxacin.

The choice of an empirical regimen requires a thorough understanding of local patterns of antibiotic resistance. Of the baseline isolates in this study, 2% were resistant to tobramycin, 9.4% were resistant to ciprofloxacin, and 14.7% were resistant to piperacillin. In general, the rate of resistance at a given institution and in a given patient reflects local patterns of antimicrobial use. As fluoroquinolone use increases for routine prophylaxis in the early chemotherapy period, often with the onset of neutropenia, fluoroquinolone must be used very carefully when fever develops and probably should be avoided, unless the antimicrobial susceptibility of the responsible organism is known.

Multiple drugs of similar spectrums are commonly used to improve the killing of possible invading organisms. However, in the current medical era of cost containment, this approach may be questioned because of appropriate concerns about the additive toxicity and the incomplete evidence of benefit from such a strategy. Multiple-drug therapy of this sort is sometimes justified by the claim that "double coverage" will prevent the emergence of resistance in this more vulnerable patient population; however, proof of the validity of this concept is at best incomplete.

The second law of thermodynamics states that the world is heading inexorably into chaos. The infectious-disease version of this principle is that we are constantly heading toward antimicrobial resistance, which will cause chaos. The question, then, is whether we can prevent chaos by one or another strategy of antibiotic use. The patient with febrile neutropenia provides an ideal opportunity to explore this and other questions, provided that we develop better diagnostic approaches and biomarkers of efficacy. A great deal of progress has been made, as shown by the low mortality rates in both of Peacock and colleagues' study groups; however, much work remains to be done. Peacock and colleagues deserve our thanks for addressing these issues with a novel combination of drugs. We need to go on from there.

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EDITORIAL

Indwelling Urinary Catheters: A One-Point Restraint?

More than four decades ago, Dr. Paul Beeson persuasively argued against routine use of indwelling urinary catheters in hospitalized patients, making the "case against the catheter" (1). He urged, "The decision to use this instrument should be made with the knowledge that it involves risk of producing a serious disease" (1). This advice remains relevant today. Although these devices provide indispensable benefits, they are also the dominant risk factor for hospital-acquired urinary tract infection, the most common nosocomial infection in the United States (2). Infections and other untoward effects associated with indwelling urinary catheters lead to increased health care costs, patient discomfort, morbidity, and even death (3–6).

Regrettably, unjustified and excessively prolonged catheter use persists despite clear evidence of its detrimental effects (7–9). Indwelling catheters have the practical effect of needlessly confining patients in what could be called a "one-point" restraint, raising serious safety and ethical concerns analogous to those noted more than a decade ago with "four-point" (limb) restraints. Lessons learned from efforts to curtail the use of physical restraints may help identify strategies for diminishing the use of indwelling urinary catheters.

INDWELLING URINARY CATHETERS ARE WIDELY—AND OFTEN INAPPROPRIATELY—USED

Each year, almost 25% of the approximately 96 million urinary catheters sold worldwide are sold in the United States, where between 16% and 25% of hospitalized patients have an indwelling urinary catheter (9, 10). In a substantial proportion of these patients, the catheter is used inappropriately (7, 8). Two decades ago, a study of hospitalized patients found that catheter use was unjustifiable for more than one third of the hospital days they were in use (8). More recently, Jain and colleagues (7) reported that initial insertion was unjustified in 21% of hospitalized patients with a urinary catheter and that continued catheter use was unwarranted for almost half of the days patients were catheterized.

Why are urinary catheters often used inappropriately? Ignorance of published recommendations (11, 12) probably accounts for part of the problem. Another reason is physician uncertainty about the patient's medical course and possible reluctance to reinsert a needed catheter. In addition, catheters may be placed and maintained for the convenience of hospital staff (4, 7), thus eliminating the need to change wet clothing or bedding, or perhaps for the prevention of skin maceration.

Finally, catheters may be used inappropriately because physicians "forget about" or were never aware of the presence of the catheter. Recently, more than one third of attending physicians and more than one quarter of resident physicians at four academic medical centers answered incorrectly when asked whether each patient on their service had a urinary catheter in place (9). The proportion of physicians unaware of the presence of a catheter was even higher for the inappropriately catheterized patients: greater than 50% of attending physicians and greater than 40% of senior residents (9). These "forgotten" catheters often remain in place until either a catheter-related complication occurs or the patient's discharge is imminent.

BURDEN OF ILLNESS ASSOCIATED WITH INDWELLING URINARY CATHETERIZATION

The incidence of bacteriuria in catheterized patients is directly related to the duration of catheterization; the daily rate of acquiring bacteriuria is approximately 3% to 10% (13). In patients with bacteriuria, 10% to 25% will develop symptoms of local urinary tract infection (3, 14), and about 3% will develop bacteremia, a serious and possibly life-threatening complication (3). Catheter-related infection is also associated with increased mortality, but whether the relationship is causal is controversial. Some argue that this infection is merely a marker of severe underlying disease. Two studies have found, however, that urinary catheter–related infection leads to an almost threefold increase in risk for death, independent of other comorbid conditions (5, 6).

Another medical consequence of catheter-related infection is increased health care costs. Each episode of hospital-acquired, symptomatic, catheter-related infection costs at least $676, and each episode of catheter-related nosocomial bacteremia costs at least $2836 (3). Thus, the cumulative economic burden of nosocomial catheter-related infection is substantial.

PATIENT RIGHTS, COMFORT, AND DIGNITY

Beyond the health and financial burden of inappropriate catheter use is the substantial patient discomfort caused by catheters. In a recent prospective study, 42% of catheterized patients reported that the indwelling catheter was uncomfortable, 48% reported that it was painful, and 61% noted that it restricted their activities of daily living (4). Two respondents provided unsolicited comments that their indwelling catheter "hurts like hell" (4). For some patients, urinary catheters operate as physical restraints, tantamount to binding them to the bed; catheters substantially and unnecessarily limit patients' ability to function freely and with dignity. Restricted activity not only reduces patient autonomy but also promotes such nosocomial complications as venous thromboembolism and pressure ulcers. Thus, we believe that the overuse of indwelling urinary catheters shares many similarities with physical restraints applied to the extremities or torso.

PHYSICAL RESTRAINTS

Physical restraints were also once common in hospitalized patients, but their use has decreased dramatically in the past decade (15). Like urinary catheters, restraints were justified as "protecting" the patient, including, ironically, from removing devices such as urinary catheters. Indeed, preventing the disruption of other therapy remains a frequent rationale for their use (15, 16). At times, restraints were used to keep patients from wandering or falling or from being injured due to agitated behavior (16). Physicians were sometimes unaware that their patients were restrained (17), and nurses frequently used restraints without a physician's order (16, 17).

Reports of death associated with physical restraints initiated a cascade of inquiries into this practice. Comprehensive studies in various clinical settings soon revealed that these devices were used frequently (18), even though they were disliked by patients (18) and were associated with nosocomial infection and pressure sores (19). With little evidence to support the use of physical restraints and substantial arguments against their use in all but the most extenuating circumstances (20), medical, nursing, public health, and administrative leaders called for change.

Health care organizations successfully decreased the use of physical restraints in various ways, including staff education and the use of committees to prospectively review the need for restraints. In the policy arena, the Omnibus Reconciliation Act of 1990 prohibited routine use of physical and chemical restraints in long-term care settings, and the Joint Commission on Accreditation of Healthcare Organizations implemented restraint-specific accreditation standards. Finally, federal regulations enacted in 1999 require that patients be free of unnecessary restraints, that restraints be used only when less restrictive interventions are ineffective, and that restraints be used only with the order of a licensed practitioner (21).

ARE INDWELLING URINARY CATHETERS A "ONE-POINT" RESTRAINT?

Limiting the use of physical restraints is a medical, organizational, and public policy success story. After recognizing the problem, health care facilities organized systematic approaches that decreased the use of physical restraints; the facilities were encouraged and sometimes compelled to do so by changes in public policy. We urge a similar multipronged approach for the overuse of indwelling urinary catheters. Few studies have carefully examined the effects of indwelling urinary catheters, especially in comparison with other means of bladder drainage or incontinence management (12); however, available data demonstrate frequent inappropriate use of and consequent harm from urinary catheters. The level of patient discomfort with this highly strategic one-point restraint is doubtless equal to or greater than the discomfort experienced with two-point or four-point extremity restraints. In our experience, physical restraint use is similar to urinary catheter use in that it is frequently initiated by nurses (7), often without a physician's order (Saint S. Unpublished data). A major difference, however, is that urinary catheters are more often crucial to patient care than are physical restraints. Therefore, policies regarding placement of indwelling catheters must reflect the important distinction between catheters that have been appropriately inserted and maintained and those that were not initially justified or were left in place for a period longer than necessary. Inappropriate restraint of patients who entrust their care to physicians, whether at four points of mobility or at one of high sensitivity, can no longer be condoned. Partly on the basis of strategies implemented to diminish the use of physical restraints, we propose the following recommendations to improve catheter use.

RECOMMENDATIONS

1. Educate all medical and nursing staff about adverse clinical consequences, patient discomfort, patient embarrassment, and activity restrictions associated with urinary catheterization.
2. Familiarize hospital personnel with the appropriate use of indwelling catheters and the availability and efficacy of other strategies and devices to manage urinary incontinence (for example, condom catheters and special undergarments).
3. Use quality-control patient audits to design institution-specific programs to decrease inappropriate use of indwelling urinary catheters.
4. Develop and evaluate the effectiveness of automatic "stop orders" for indwelling urinary catheters; these orders should require that the catheter either be removed or reordered after a specified period of catheterization (for example, after 48 hours).
5. The Joint Commission on Accreditation of Healthcare Organizations and other regulatory bodies should consider developing strategies regarding inappropriate use of indwelling urethral catheters for health care organizations.

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Imaging His Pain

His finger circled, and circled
the ecchymosis.
Here,
it hurts here,
deep under the ribs,
not the ribs,
no not the ribs,
they don't hurt, not at all,
see,
I can punch them,
no pain.
When the red spot it came up,
then I knew,
I knew I must have an infection deep in an organ,
deep in an organ,
not here on the surface,
not the ribs,
see they don't hurt.
Three weeks,
it's always there,
doesn't go away.
can't sleep on my left side,
hurts too much here,
it hurts here,
deep in an organ,
I know I've got an infection deep in an organ.

We scanned the site with X-rays
to visualize the source of his pain.
Nothing there,
nothing in his left lower chest area. But—
the radiograph showed instead
a huge mass in his right suprahilar area,
a subcarinal density, and
peripheral nodules in both lung fields.
Chest and abdominal CT scans confirmed
nothing
at the site of his pain.

The chest X-ray hangs on the view box,
light shining through the lesions,
darkness where his finger circled minutes ago. But—
his pain is there,
deep in organ space,
so deep X-rays can't penetrate it,
so deep I can't transilluminate it.
I stare at the black and white image of his innards.
The tumors radiate,
suns burning my retina,
leaving scars,
permanent blind spots
that sense his eclipse
by pain.

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Screening for Colorectal Cancer: Recommendation and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendation on screening for colorectal cancer and the supporting scientific evidence and updates the 1995 recommendations contained in the *Guide to Clinical Preventive Services*, 2nd edition. At that time, the USPSTF recommended screening for colorectal cancer with annual fecal occult blood testing, periodic sigmoidoscopy, or the combination of fecal occult blood testing and sigmoidoscopy but concluded that the evidence was insufficient to recommend for or against colonoscopy or barium enema.

The complete USPSTF recommendation and rationale statement on this topic, which includes a brief review of the supporting evidence, is available through the USPSTF Web site (www.preventiveservices.ahrq.gov), the National Guideline Clearinghouse (www.guideline.gov), and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (telephone, 800-358-9295; e-mail, ahrqpubs@ahrq.gov). The complete information on which this statement is based, including tables and references, is available in the accompanying article in this issue and in the summary of the evidence and systematic evidence review on the Web sites already mentioned.

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See related articles on pp 96-104 and pp 132-141.

* For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

SUMMARY OF THE RECOMMENDATION

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians screen all men and women 50 years of age or older for colorectal cancer. This is a **grade A recommendation.** (See **Appendix** Table 1 for a description of the USPSTF classification of recommendations.)

The USPSTF found fair to good evidence that several screening methods are effective in reducing mortality from colorectal cancer. The USPSTF concluded that the benefits from screening substantially outweigh potential harms, but the quality of evidence, magnitude of benefit, and potential harms vary with each method.

The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality. The USPSTF did not find direct evidence that screening colonoscopy is effective in reducing colorectal cancer mortality rates; efficacy of colonoscopy is supported by its integral role in trials of FOBT, extrapolation from sigmoidoscopy studies, limited case–control evidence, and the ability of colonoscopy to inspect the proximal colon. Double-contrast barium enema offers an alternative means of whole-bowel examination, but it is less sensitive than colonoscopy and there is no direct evidence that it is effective in reducing mortality rates. The USPSTF found insufficient evidence that newer screening techniques (for example, computed tomographic colography) are effective in improving health outcomes. (See **Appendix** Table 2 for a description of the USPSTF classification of levels of evidence.)

There are insufficient data to determine which screening strategy is best in terms of the balance of benefits and potential harms or cost-effectiveness. Studies reviewed by the USPSTF indicate that colorectal cancer screening is likely to be cost-effective (<$30 000 per additional year of life gained) regardless of the strategy chosen.

It is unclear whether the increased accuracy of colonoscopy compared with alternative screening methods (for example, the identification of lesions that FOBT and flexible sigmoidoscopy would not detect) offsets the procedure's additional complications, inconvenience, and costs.

CLINICAL CONSIDERATIONS

Potential screening options for colorectal cancer include home FOBT, flexible sigmoidoscopy, the combination of home FOBT and flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema. Each option has advantages and disadvantages that may vary for individual patients and practice settings. The choice of specific screening strategy should be based on patient preferences, medical contraindications, patient adherence, and available resources for testing and follow-up. Clinicians should talk to patients about the benefits and potential harms associated with each option before selecting a screening strategy.

The optimal interval for screening depends on the test. Annual FOBT offers greater reductions in mortality rates than biennial screening but produces more false-positive results. A 10-year interval has been recommended for colonoscopy on the basis of evidence regarding the natural history of adenomatous polyps. Shorter intervals (5 years) have been recommended for flexible sigmoidoscopy and double-contrast barium enema because of the lower sensitivity of these methods, but there is no direct evidence with which to determine the optimal interval for tests other than FOBT. Case–control studies have suggested that sigmoidoscopy every 10 years may be as effective as sigmoidoscopy performed at shorter intervals.

The USPSTF recommends initiating screening at 50 years of age for men and women at average risk for colorectal cancer, based on the incidence of cancer above this age in the general population. In persons at higher risk (for example, those with a first-degree relative who receives a diagnosis of colorectal cancer before 60 years of age), initiating screening at an earlier age is reasonable.

Expert guidelines exist for screening very high-risk patients, including those with a history suggestive of familial polyposis or hereditary nonpolyposis colorectal cancer or those with a personal history of ulcerative colitis (1). Early screening with colonoscopy may be appropriate, and genetic counseling or testing may be indicated for patients with genetic syndromes.

The appropriate age at which colorectal cancer screening should be discontinued is not known. Screening studies have generally been restricted to patients younger than 80 years of age, with colorectal cancer mortality rates beginning to decrease within 5 years of initiating screening. Yield of screening should increase in older persons (because of higher incidence of colorectal cancer), but benefits may be limited as a result of competing causes of death. Discontinuing screening is therefore reasonable in patients whose age or comorbid conditions limit life expectancy.

Proven methods of FOBT screening use guaiac-based test cards that patients prepare at home from three consecutive stool samples and forward to the clinician. Whether patients need to restrict their diet and avoid certain medications is not established. Rehydration of the specimens before testing increases the sensitivity of FOBT but substantially increases the number of false-positive results. Neither digital rectal examination nor the testing of a single stool specimen obtained during digital rectal examination is recommended as an adequate screening strategy for colorectal cancer.

The combination of FOBT and sigmoidoscopy may detect more cases of cancer and more large polyps than either test alone, but the additional benefits and potential harms of combining the two tests are uncertain. In general, FOBT should precede sigmoidoscopy because a positive result is an indication for colonoscopy, obviating the need for sigmoidoscopy.

Colonoscopy is the most sensitive and specific test for detecting cancer and large polyps but is associated with higher risks than other screening tests for colorectal cancer. These include a small risk for bleeding and risk for perforation, primarily associated with removal of polyps or with biopsies performed during screening. Colonoscopy also usually requires more highly trained personnel, overnight bowel preparation, sedation, and longer recovery time (which may necessitate transportation for the patient). It is not certain whether the potential added benefits of colonoscopy relative to screening alternatives are large enough to justify the added risks and inconvenience for all patients.

Initial costs of colonoscopy are higher than the costs of other tests. Estimates of cost-effectiveness, however, suggest that, from a societal perspective, compared with no screening, all methods of screening for colorectal cancer are likely to be as cost-effective as other clinical preventive services—less than $30 000 per additional year of life gained. The brief review of the evidence that is normally included in USPSTF recommendations is available in the complete Recommendation and Rationale statement on the USPSTF Web site (www.preventiveservices.ahrq.gov).

RECOMMENDATIONS OF OTHERS

The American Cancer Society recommends screening people at average risk for colorectal cancer beginning at 50 years of age by 1) FOBT annually, 2) flexible sigmoidoscopy every 5 years, 3) annual FOBT plus flexible sigmoidoscopy every 5 years, 4) double-contrast barium enema every 5 years, or 5) colonoscopy every 10 years (2). The American Cancer Society does not recommend digital rectal examination as a stand-alone screening test for colorectal cancer. Similar recommendations are issued by the American College of Surgeons, the American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians (3–5). The American Gastroenterological Association, as part of a consortium of related professional organizations, also issues similar recommendations, which are currently being updated (1). The American College of Physicians–American Society of Internal Medicine does not have current guidelines on screening. The Canadian Task Force on Preventive Health Care concludes that there is good evidence to recommend annual or biennial FOBT and fair evidence to recommend sigmoidoscopy as part of the periodic health examination in average-risk adults after 50 years of age; evidence is insufficient to recommend for or against colonoscopy or combined FOBT and sigmoidoscopy (6).

APPENDIX

Members of the U.S. Preventive Services Task Force are Alfred O. Berg, MD, MPH, *Chair* (University of Washington, Seattle, Washington); Janet D. Allan, PhD, RN, CS, *Vice-Chair* (University of Texas Health Science Center, San Antonio, Texas); Paul S. Frame, MD (Tri-County Family Medicine, Cohocton, and University of Rochester, Rochester, New York); Charles J. Homer, MD, MPH (National Initiative for Children's Healthcare Quality, Boston, Massachusetts); Mark S. Johnson, MD, MPH (University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey); Jonathan D. Klein, MD, MPH (University of Rochester School of Medicine, Rochester, New York); Tracy A. Lieu, MD, MPH (Harvard Pilgrim Health Care and Harvard Medical School, Boston, Massachusetts); Cynthia D. Mulrow, MD, MSc (University of Texas Health Science Center, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Texas); C. Tracy Orleans, PhD (The Robert Wood Johnson Foundation, Princeton, New Jersey); Jeffrey F. Peipert, MD, MPH (Women and Infants' Hospital, Providence, Rhode Island); Nola J. Pender, PhD, RN (University of Michigan, Ann Arbor, Michigan); Albert L. Siu, MD, MSPH (Mount Sinai School of Medicine and The Mount Sinai Medical Center, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Company, Inc., West Point, Pennsylvania); Carolyn Westhoff, MD, MSc (Columbia University College of Physicians and Surgeons, New York, New York); and Steven H. Woolf, MD, MPH (Virginia Commonwealth University, Fairfax, Virginia).

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Appendix Table 1. **U.S. Preventive Services Task Force Grades and Recommendations***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

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Screening for Colorectal Cancer in Adults at Average Risk: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Purpose: **To assess the effectiveness of different colorectal cancer screening tests for adults at average risk.**

Data Sources: **Recent systematic reviews; *Guide to Clinical Preventive Services*, 2nd edition; and focused searches of MEDLINE from 1966 through September 2001. The authors also conducted hand searches, reviewed bibliographies, and consulted context experts to ensure completeness.**

Study Selection: **When available, the most recent high-quality systematic review was used to identify relevant articles. This review was then supplemented with a MEDLINE search for more recent articles.**

Data Extraction: **One reviewer abstracted information from the final set of studies into evidence tables, and a second reviewer checked the tables for accuracy. Discrepancies were resolved by consensus.**

Data Synthesis: **For average-risk adults older than 50 years of age, evidence from multiple well-conducted randomized trials supported the effectiveness of fecal occult blood testing in reducing colorectal cancer incidence and mortality rates compared with no screening. Data from well-conducted case–control studies supported the effectiveness of sigmoidoscopy and possibly colonoscopy in reducing colon cancer incidence and mortality rates. A nonrandomized, controlled trial examining colorectal cancer mortality rates and randomized trials examining diagnostic yield supported the use of fecal occult blood testing plus sigmoidoscopy. The effectiveness of barium enema is unclear. Data are insufficient to support a definitive determination of the most effective screening strategy.**

Conclusions: **Colorectal cancer screening reduces death from colorectal cancer and can decrease the incidence of disease through removal of adenomatous polyps. Several available screening options seem to be effective, but the single best screening approach cannot be determined because data are insufficient.**

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For author affiliations, see end of text.
See related articles on pp 96-104 and pp 129-131.

The U.S. Preventive Services Task Force (USPSTF) last considered its recommendations regarding colorectal cancer screening in 1996 (1). At that time, the available evidence included one randomized, controlled trial showing that fecal occult blood testing (FOBT) reduced mortality rates (2); a case–control study showing that persons having sigmoidoscopy were less likely to die of colorectal cancer (3); and one nonrandomized, controlled trial of FOBT combined with rigid sigmoidoscopy that suggested some benefit from the two tests together (4). On the basis of this evidence, the USPSTF recommended screening for colorectal cancer with FOBT, sigmoidoscopy, or both (a grade B recommendation) but did not recommend for or against other means of screening (digital rectal examination, double-contrast barium enema, or colonoscopy) because the available evidence was insufficient. (See the companion article in this issue for a description of the USPSTF classification of recommendations.) The Task Force also recommended that FOBT be performed yearly but did not specify an interval for sigmoidoscopy.

Since 1996, important new evidence has emerged regarding the effectiveness of colorectal cancer screening. We performed an updated systematic review to help the USPSTF evaluate new evidence on the effectiveness of different colorectal cancer screening tests as it updated its previous recommendation. We examined the evidence concerning the effectiveness of screening in adults older than 50 years of age who are at average risk for colorectal cancer. The effectiveness, accuracy, and adverse effects of digital rectal examination (with or without a single office-based FOBT), traditional three-card FOBT (hereafter referred to as FOBT), sigmoidoscopy, FOBT with sigmoidoscopy, double-contrast barium enema, and colonoscopy were examined. Other tests or combinations of tests have not been well evaluated and are not discussed here. A more detailed report of our review can be found on the Web site of the U.S. Agency for Healthcare Research and Quality (www.ahrq.gov/clinic/uspstfix.htm) (5). The USPSTF's updated recommendations for colorectal cancer screening recommendations can be found in the companion article in this issue (6).

METHODS

To identify the relevant literature, we used the *Guide to Clinical Preventive Services*, 2nd edition (1); existing systematic reviews; focused MEDLINE literature searches from 1966 through September 2001; and hand searches of key articles. When available, systematic reviews were used to identify older relevant studies. Literature searches were used to identify newer studies. Detailed descriptions of the literature searches can be found in the Appendix (available at www.annals.org).

To identify relevant studies, one reviewer examined the abstracts of the articles identified in the initial search. A second reviewer examined the excluded articles. Disagreements about inclusion were resolved by consensus. Two reviewers examined the full text of the remaining articles to determine final eligibility. We used evidence from randomized, controlled trials or observational studies that measured patient outcomes, particularly changes in colorectal cancer mortality rates and incidence. When such data were not available, we included indirect information on the accuracy of screening tests. Details about study inclusion are available in the Appendix (available at www.annals.org). We rated the quality of the included articles by using the criteria developed by the USPSTF Methods group (7), which are described in the accompanying article in this issue (6). We used the final set of eligible articles to create evidence tables and a draft report. The draft report was extensively peer reviewed by the USPSTF, experts in the field, governmental agencies, and nongovernmental organizations.

This evidence report was funded through a contract to the Research Triangle Institute–University of North Carolina Evidence-based Practice Center from the Agency for Healthcare Research and Quality. Staff of the funding source contributed to the study design, reviewed draft and final manuscripts, and made editing suggestions.

RESULTS

Our general search identified 719 articles published since 1995 on colorectal cancer screening. We retained 19 of these articles in our final document. Specific searches from 1966 through 2001 for articles about the accuracy of barium enema and complications of screening yielded 621 and 839 articles, respectively. After review, we retained 13 articles about barium enema and 19 articles about complications of screening. We also included 15 articles identified from the previous USPSTF review or from hand searches of other articles. **Table 1** summarizes our findings.

Digital Rectal Examination

Effectiveness

A case–control study from the Kaiser Permanente Medical Care Program in northern California examined the effect of screening with digital rectal examination on death from colorectal cancer (8). The investigators identified patients 45 years of age and older who died of distal rectal cancer between 1971 and 1986 and selected matched controls from the patient membership. They examined medical records to determine whether the patients and controls had undergone screening digital rectal examination within a year of cancer diagnosis. Investigators found no difference between groups after controlling for potential confounders, although the confidence interval was wide (odds ratio, 0.96 [95% CI, 0.56 to 1.7]).

Accuracy

The potential sensitivity of screening digital rectal examination is low; fewer than 10% of cases of colorectal cancer are within reach of the examining finger (28). The specificity of positive results on digital rectal examination has not been examined in outpatients at average risk for colorectal cancer.

In-Office Fecal Occult Blood Testing after Digital Rectal Examination

Effectiveness

No studies have examined the effect of a single in-office FOBT after digital rectal examination on colorectal cancer incidence or mortality rates.

Accuracy

A single in-office FOBT is likely to be less sensitive than the traditional three-card FOBT performed at home because only one sample is taken (9). In a large study from Japan, Yamamoto and Nakama (10) found that the first test card detected only 58% of cancer found after a three-card test. The single in-office FOBT may be less specific than a properly performed three-card FOBT because the in-office test does not allow degradation of the vegetable peroxidases that sometimes produce false-positive results (9). In addition, the potential trauma from the in-office examination itself may also result in lower specificity (9). Two studies of poor to fair quality that used existing data to retrospectively compare the specificity of the single in-office FOBT and the three-card home FOBT (11, 12) found little difference in specificity between the two groups. However, the validity of these studies is limited because neither could ensure that similar patient samples received each test.

Fecal Occult Blood Testing

Effectiveness

In addition to an older randomized trial performed in Minnesota (2), which was available to the USPSTF in 1996, two newer randomized, controlled trials have examined the effectiveness of biennial FOBT for reducing death from colorectal cancer (13, 14). These more recent trials, from the United Kingdom (13) and Denmark (14), found 15% and 18% reductions in mortality rates, respectively, with biennial testing. Neither trial used slides that were rehydrated before development (**Table 2**).

The Minnesota trial compared annual and biennial testing with no screening and rehydrated most test cards (83%). Cumulative colorectal cancer mortality rates after 18 years of follow-up were 33% (CI, 17% to 49%) lower among persons randomly assigned to undergo annual FOBT than in a control group that was not offered screening (absolute rates, 9.5 deaths per 1000 participants vs. 14.1 deaths per 1000 participants; difference, 4.6 deaths per 1000 participants) (2). Biennial screening, which did not show a reduction in mortality rates at 13-year follow-up, produced a 21% (CI, 3% to 38%) reduction in mortality rate at 18 years (15). The 18-year follow-up also showed that the incidence of colorectal cancer decreased by 20% (CI, 10% to 30%) and 17% (CI, 6% to 27%) in the groups screened annually and biennially, respectively, compared with controls (16). Because of differences in hydration, test frequency, duration, and effect size, the results of these trials could not be combined in a meta-analysis.

Table 1. **Characteristics of Screening Tests for Colorectal Cancer***

Screening Strategy for CRC	Effectiveness in Reducing Incidence of and Death from CRC	Evidence Grade†	Ability To Detect Cancer	Evidence Grade†
Digital rectal examination	Case–control study found no difference in mortality rates; OR, 0.96 [0.56–1.7] (8)	Level II—poor	Pathologic data suggest <10% of CRC is within reach of examining finger	
Office FOBT (one card)	Unknown		Only 58% of cancer cases are detected on the first of three cards, suggesting lower sensitivity than three-card testing (10)	Level III—fair
Home FOBT (three cards), unrehydrated	Biennial testing: 2 trials found mortality reductions of 15% [1%–26%] (13) and 18% [1%–32%] (14)	Level I—good	One-time sensitivity 30%–40% Unrehydrated FOBT finds about 25% of cancer cases (9)	
Home FOBT (three cards), rehydrated	Annual testing: 33% [13%–50%] reduction in mortality (2); 20% [10%–30%] reduction in cancer incidence (16) Biennial testing: 21% [3%–38%] reduction in mortality (15); 17% [6%–27%] reduction in cancer incidence (16)	Level I—good	Single-test accuracy 50% [30%–70%] for cancer, 24% [19%–29%] for advanced neoplasms (17) Over 13 years, rehydrated FOBT finds 50% of cancer cases (2)	Level III—good
Sigmoidoscopy	Small RCT found decreased CRC mortality rates with screening; RR, 0.50 [0.10–2.72] (18) Case–control studies suggest a 59% [31%–75%] reduction in mortality rate within reach of scope (3)	Level I—fair Level II—good	One-time screening detects 68%–78% of advanced neoplasia (17, 20)	Level III—good
Combined FOBT and sigmoidoscopy	Nonrandomized trial found a 43% reduction in mortality rate when FOBT was added to rigid sigmoidoscopy; RR, 0.57 [0.56–1.19] (4)	Level I—fair to poor	One-time screening detects 76% of advanced neoplasia (17) Increased yield when sigmoidoscopy is added to FOBT (21-23)	Level III—good
Double-contrast barium enema	Unknown		Sensitivity of one-time test for cancer or large polyps, 48% [24%–67%] (24)	Level III—fair
Colonoscopy	Case–control study found an OR of 0.43 [0.30–0.63] for death from CRC; CRC incidence decreased by 40%–60% (26)	Level II—fair	Sensitivity for large adenomas >90%; sensitivity for cancer probably higher (27)	Level III—good

* CRC = colorectal cancer; FOBT = fecal occult blood test; NA = not applicable (see text); OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk. Numbers in square brackets are 95% CIs; numbers in parentheses are reference numbers.

† Level I = evidence from one or more controlled trials; level II = evidence from cohort or case–control studies; level III = evidence from diagnostic accuracy studies or case series. For each level, the investigators have assigned a quality score based on methods described in reference 7.

Accuracy

A systematic review from 1997 found that the sensitivity of a single unrehydrated FOBT for cancer was approximately 40%; its specificity seems to range from 96% to 98%. Rehydration was found to increase sensitivity to between 50% and 60% but decreased specificity to 90% (9, 29). In a recent study, Lieberman and colleagues (17) found that the sensitivity of rehydrated FOBT for cancer was 50% (CI, 30% to 70%). For advanced neoplasia (cancer and polyps that are large, villous, or dysplastic), sensitivity was 24% (CI, 19% to 29%) and specificity was 94% (CI, 93% to 95%).

In the annual screening arm of the 13-year Minnesota trial, which primarily used rehydrated test cards and had a high initial rate of participation (approximately 90%), 49% of patients who developed colorectal cancer were identified through screening. Thirty-eight percent of all patients had had at least one colonoscopy (2). Biennial screening detected 39% of patients with cancer in the intervention group, and 28% of patients required colonoscopy. Compared with the Minnesota trial, the two European trials were population-based, lasted 8 to 10 years, used only biennial testing, and had lower participation rates (60% to 70% of patients completed the first screening). Screening detected 27% of patients in the intervention group who developed colorectal cancer, and only 5% of patients had colonoscopy (13, 14).

Adverse Effects

Fecal occult blood testing itself has few adverse effects, but false-positive results lead to further tests, such as colonoscopy, during which adverse effects may occur. The specific adverse effects of colonoscopy are described later in this review. Theoretically, a previously negative result on FOBT could falsely reassure patients and lead to delayed response to the development of colorectal symptoms if cancer were to develop, but this concern has not been evaluated empirically.

Sigmoidoscopy

Effectiveness

Thiis-Evensen and coworkers (18) performed a small randomized trial of sigmoidoscopy screening in Norway. In 1983, 799 men and women who were 50 to 59 years of age and were drawn from a population registry were randomly assigned to receive screening flexible sigmoidoscopy (400 patients) or no screening (399 patients). Eighty-one percent of those offered flexible sigmoidoscopy accepted.

Table 1—Continued

Chance of False-Positive Results	Evidence Grade†	Adverse Effects	Evidence Grade†
Unknown		No direct adverse effects known	
Little difference compared with three-card testing (11, 12)	Level III—poor	No direct adverse effects known	
Single-test specificity 96%–98% 5%–10% of patients will require colonoscopy over 10 years of biennial testing (9)	Level III—good	No direct adverse effects known	
Single-test specificity 90% Over 10 to 13 years, 38% of patients tested annually and 28% tested biennially with rehydrated FOBT required colonoscopy (2)	Level III—good	Inconvenience, adverse events resulting from follow-up tests after positive results	
NA		Perforation rate for diagnostic examinations <1 in 10 000; bleeding in 2.5% of patients after diagnostic studies, 5.5% after procedures with polypectomy (19)	Level III—good
NA		Sum of adverse effects from each test alone	
One-time specificity, 85%, [82%–88%] (24)	Level III—fair	Perforation rate 1 in 25 000 in a study with screening and symptomatic patients (25)	Level III—poor
NA		Diagnostic procedures: perforation rate 1 in 2000 Polypectomy: perforation rate 1 in 500–1000; bleeding rate 1 in 100–500; mortality rate 1 in 20 000 (5)	Level III—fair to good

All patients found to have polyps on sigmoidoscopy underwent immediate diagnostic colonoscopy and had surveillance examinations 2 and 6 years later. Over the 13 years of the trial, two cases of colorectal cancer were diagnosed in the intervention group and 10 were diagnosed in the control group (relative risk for colorectal cancer, 0.2 [CI, 0.03 to 0.95]). One person who was assigned to the intervention group but never had sigmoidoscopy died of colorectal cancer, as did three controls (relative risk, 0.50 [CI, 0.10 to 2.72]). Overall mortality rate was higher in the intervention group than in the control group (14% vs. 9%; relative risk, 1.57 [CI, 1.03 to 2.40]), mostly because of an excess of cardiovascular deaths. No clear relationship emerged between excess deaths and any procedure-related complications.

Two ongoing randomized trials using flexible sigmoidoscopy will report their initial results within 5 years. One trial in the United Kingdom is examining the effect of screening with sigmoidoscopy once per lifetime (19), and a second trial in the United States is examining sigmoidoscopy screening every 5 years in patients who are assumed to be receiving FOBT as part of usual care (30).

Two older, well-designed case–control studies that provide other important information on the effectiveness of sigmoidoscopy screening were available to the USPSTF in 1996. Using data from the Kaiser Permanente Medical Care Program in northern California, Selby and associates (3) found that rigid sigmoidoscopy had been performed in 9% of persons who died of colorectal cancer occurring within 20 cm of the anus and in 24% of persons who did not die of cancer occurring within 20 cm of the anus. The adjusted odds ratio of 0.41 (CI, 0.25 to 0.69) suggested that sigmoidoscopy screening reduced the risk for death by 59% for cancer within reach of the rigid sigmoidoscope.

The investigators noted that the adjusted odds ratio was 0.96 for proximal colon cancer that was beyond the reach of the sigmoidoscope (3). This finding added support to the hypothesis that the reduced risk for death from cancer within reach of the rigid sigmoidoscope could be attributed to screening rather than to confounding factors. The risk reduction associated with sigmoidoscopy screening did not diminish during the first 9 to 10 years after the test was performed. The study by Selby and associates mostly used rigid sigmoidoscopes. However, in another case–control study supporting the effectiveness of sigmoidoscopy, 75% of the examinations were performed with a flexible instrument (31).

Accuracy

Two recent studies have examined the sensitivity of screening sigmoidoscopy for cancer or advanced adenomas.

Table 2. **Trials of Fecal Occult Blood Testing**

Trial Characteristics	**Trial (Reference)**		
	Minnesota (2)	**United Kingdom (13)**	**Denmark (14)**
Frequency of testing	Annual and biennial	Biennial	Biennial
Participants, *n*	>45 000 men and women	>150 000 men and women	>60 000 men and women
Age, *y*	50–80	45–74	45–74
Duration of follow-up, *y*	18 (annual and biennial)	8	10
Hydration of slides	Yes (83%)	No	No
Participation rate, %*	90 (annual and biennial)	60	67
Patients requiring colonoscopy, %	38 (annual); 28 (biennial)	5	5
Positive predictive value, %	1.9 (annual); 2.7 (biennial)†	10–12	8–18
Relative risk reduction for death from colorectal cancer [95% CI], %	33 [17–49] (annual); 21 [3–38] (biennial)	15 [1–26]	18 [1–32]
Absolute risk reduction for death from colorectal cancer per 1000 participants	4.6 (annual); 2.9 (biennial)	0.8	1.4

* Participation was defined as completion of at least one test.
† Mostly rehydrated slides (83%).

in healthy patients, using colonoscopy as the criterion standard. They found that sigmoidoscopy would identify 70% to 80% of patients with advanced adenomas or cancer (17, 20). Sigmoidoscopy can produce false-positive results by detecting hyperplastic polyps that do not have malignant potential or adenomatous polyps that are unlikely to become malignant during the patient's lifetime. Because studies of diagnostic accuracy cannot measure whether small or large adenomas that are identified and removed would have become cancer, it is not possible to classify such findings in terms of accuracy in detecting cancer. In practice, most investigators consider all adenomas to be "true positives" regardless of whether they would ever progress to cancer. Comparison of the specificity of sigmoidoscopy with that of nonendoscopic screening methods, such as FOBT and barium enema, is therefore difficult.

Adverse Effects

Estimates of bowel perforations from sigmoidoscopy have generally been in the range of 1 to 2 or fewer per 10 000 examinations, particularly since the introduction of the flexible sigmoidoscope (32). Atkin and colleagues (19) recently reported initial results from a trial of sigmoidoscopy screening in which experienced endoscopists performed sigmoidoscopy in 1235 asymptomatic adults 55 to 64 years of age. Two hundred eighty-eight patients had polyps removed during the examination. Adverse effects, including pain, anxiety, or any degree of bleeding, were assessed by a written questionnaire immediately after the test and by a mailed questionnaire 3 months later. Of all patients, 3.2% (40 of 1235) reported bleeding, 16 of 288 (5.5%) after polypectomy and 24 of 947 (2.5%) after diagnostic studies. One patient required hospital admission, and no patients required a transfusion. Fourteen percent of patients reported moderate pain, and 0.4% reported severe pain. More than 25% of patients reported gas or flatus. No perforations were reported, but one patient died of peritonitis after a complicated open surgical procedure to remove a severely dysplastic adenoma. A recent study of endoscopic complications from the Mayo Clinic in Arizona identified two perforations in 49 501 sigmoidoscopy procedures (33).

Fecal Occult Blood Test and Sigmoidoscopy

Effectiveness

Currently, no randomized trials that examine death from colorectal cancer as an end point have compared FOBT alone or sigmoidoscopy alone with a strategy of performing both tests. In 1992, Winawer and coworkers (4) conducted a nonrandomized trial of more than 12 000 first-time attendees at a preventive health clinic in New York. This trial was available to the USPSTF in 1996. The control group received rigid sigmoidoscopy at the first visit, and all study participants were invited to return for annual reexamination with rigid sigmoidoscopy. Patients in the intervention group received rigid sigmoidoscopy and were also asked to complete Hemoccult (Beckman Coulter, Fullerton, California) FOBT cards. Patients who had adenomas larger than 3 mm on sigmoidoscopy or who had positive results on FOBT underwent full colonic examination with barium enema and colonoscopy. The control group received rigid sigmoidoscopy at the first visit, and participants were invited to return for annual reexamination. Few patients continued to participate after the first examination (20% had FOBT at year 2, 15% at year 3). Incidence of colorectal cancer and death were assessed over a 9-year period, and follow-up data were available for 97% of patients.

Demographic and clinical data suggest that the groups were comparable, despite the absence of randomization. More cases of colorectal cancer were detected on initial examination in intervention patients than in control patients (4.5 per 1000 participants vs. 2.5 per 1000 participants). Incidence rates (cancer detected after the initial examination) were similar between groups (0.9 per 1000 person-years in each group). Incidence of death from colorectal cancer was 0.36 per 1000 patient-years in the intervention group and 0.63 per 1000 patient-years among controls (relative risk, 0.56 [CI, 0.25 to 1.19]).

Fecal occult blood testing combined with rigid sigmoidoscopy seems to increase the yield of initial screening and may reduce mortality rates. Because rigid sigmoidoscopy is no longer used for screening, the generalizability of these results to the use of FOBT plus flexible sigmoidoscopy is unclear. Whether the incremental yield of combined screening will change after additional rounds of testing also remains uncertain.

Accuracy

Recent randomized trials from Europe examined the additional diagnostic yield of performing sigmoidoscopy plus FOBT at one point in time for patients who were not already part of an ongoing screening program (21–23). In each study, adding sigmoidoscopy to FOBT increased the identification of significant adenomas or cancer by a factor of two or more. Adding FOBT to sigmoidoscopy did not seem to identify any additional significant lesions. Winawer and coworkers (4), however, found an increased yield from adding FOBT to rigid sigmoidoscopy. In each study, data were limited to a single round of testing. The additional yield of this strategy may be lower after the first round of testing, but the impact of this strategy on mortality rates has not been fully evaluated.

Adverse Effects

The adverse effects of FOBT plus sigmoidoscopy are equal to the adverse effects of each test alone.

Double-Contrast Barium Enema

Effectiveness

We identified no published studies that examined the effectiveness of double-contrast barium enema in reducing incidence of or death from colorectal cancer. Several studies have examined the accuracy of double-contrast barium enema for diagnosing colorectal cancer or adenomatous polyps (24, 34–43). Most are of methodologically poor quality, however, because they examined patients with symptoms or did not prospectively collect blinded data.

The National Polyp Study is a randomized trial of different intervals of surveillance after polypectomy (examinations at 1 and 3 years vs. at 3 years only). In a substudy of this trial, Winawer and colleagues (24) compared the accuracy of double-contrast barium enema with that of colonoscopy. The sensitivity of double-contrast barium enema was 32% (CI, 25% to 39%) for polyps smaller than 0.5 cm; 53% (CI, 40% to 66%) for polyps 0.6 to 1 cm; and 48% (CI, 24% to 67%) for polyps larger than 1 cm, including two cases of cancerous polyps. Results of double-contrast barium enema were positive in 83 of 470 patients in whom colonoscopy detected no polyps (specificity, 85% [CI, 82% to 88%]).

Winawer and colleagues (24) examined patients who previously had colonoscopy and removal of all polyps. Their results, therefore, may have limited generalizability for screening because screening largely involves persons who have not had recent colonoscopic examination and polypectomy and therefore may be more likely to have large polyps or tumors. However, the low sensitivity for large polyps and tumors reported by Winawer and colleagues is cause for concern and may limit the potential effectiveness of screening with double-contrast barium enema.

Adverse Effects

The estimated risk for perforation during barium enema is low. Kewenter and Brevinge (44) found that no perforations or other complications occurred among 1987 screening patients undergoing barium enema as part of a screening work-up. Blakeborough and associates (25) surveyed radiologists in the United Kingdom about complications of barium enema during a 3-year period (1992 through 1994). All examinations were included, regardless of the indication for the procedure. Important complications of any type occurred in 1 in 10 000 examinations. Perforation occurred in 1 of 25 000 examinations, and death occurred in 1 in 55 000 examinations, although it is not clear whether all deaths were procedure related.

Colonoscopy

Effectiveness

The ability of colonoscopy to prevent colorectal cancer or death has not been measured in a screening trial. The National Polyp Study estimated that 76% to 90% of cancer could be prevented by regular colonoscopic surveillance examinations, based on comparison with historic controls (45). However, these results should be interpreted with caution. The comparison groups were not from the same underlying population, which could introduce bias. In addition, all trial participants had polyps detected and removed, limiting generalizability of the results to the average screening population.

Müller and Sonnenberg (26), in a case–control study at Veterans Affairs hospitals, found that patients with a diagnosis of colorectal cancer were less likely to have had previous colonoscopy. The odds ratios for disease incidence were 0.47 (CI, 0.37 to 0.58) for colon cancer and 0.61 (CI, 0.48 to 0.77) for rectal cancer. For death from colorectal cancer, the odds ratio was also lower for patients with previous colonoscopy (odds ratio, 0.43 [CI, 0.30 to 0.63]).

Accuracy

Because colonoscopy is commonly used as the criterion standard examination, it is difficult to calculate its sensitivity. Using tandem colonoscopic examinations, Rex and colleagues (27) found single-test sensitivity to be 90% for large adenomas and 75% for small adenomas (<1 cm); sensitivity for cancer probably exceeds 90%.

Recent identification of flat lesions that can be missed on regular colonoscopy suggests that some histologic variants do not progress through the typical adenoma–carcinoma development sequence and thus may not be easily detectable in the precancerous phase (46). If flat lesions account for 10% of all adenomas, sensitivity of all endoscopic screening methods may be lower than previously thought.

The specificity of colonoscopy with biopsy is generally reported to be 99% or 100%, but this assumes that all detected adenomas represent true-positive results. As with sigmoidoscopy, most detected adenomas, especially small adenomas, will never develop into cancer. If detection of an adenoma that will not become cancer is considered a false-positive result that subjects a patient to risk without benefit, then the actual specificity of colonoscopy would be much lower.

Adverse Effects

Colonoscopy, which uses sedation and requires skilled support personnel, is more expensive and has a higher risk for procedural complications than other screening tests, particularly when polypectomy is performed. Use of conscious sedation adds the risk for complications attributable to the sedative agent. In our systematic review of studies examining the principal complications of colonoscopy (5), we focused on hemorrhage and perforation but noted the less frequent complications of death, infections, sedation-related events, and chemical colitis. Two recent studies examined the incidence of complications from colonoscopy performed in screening populations. Lieberman and associates (17), in a study in patients in Veterans Affairs medical centers, found that 10 of 3121 patients (0.3%) had major complications during or immediately after the procedures. Of these 10 patients, 6 had bleeding that required hospitalization and 1 each had a stroke, myocardial infarction, Fournier gangrene, and thrombophlebitis. Three other patients died within 1 month, probably of causes unrelated to the procedure. In a study of employees of a large corporation, Imperiale and coworkers (20) found that among 1994 persons 50 years of age and older who underwent colonoscopy, 1 (0.05%) had a perforation that did not require surgery and 3 (0.15%) had bleeding that required emergency department visits but not admission or surgery.

Apart from these two screening studies, most of the studies examining colonoscopy complications are retrospective reviews of endoscopy records from U.S. university hospitals that recorded only immediate complications and included a mixture of screening and diagnostic procedures (17, 20, 33, 47–61). A prospective study that also included a patient questionnaire administered 10 days after the procedure identified several additional important complications that occurred outside the hospital, suggesting that hospital record review alone may underestimate actual complication rates (47).

Despite these limitations, these studies provide a useful approximation of the complication rates that can be expected from colonoscopy. For diagnostic procedures, perforation rates were low (0.029% to 0.61%). Bleeding was not reported in enough studies to generate an estimate of its frequency. For therapeutic procedures, complication rates were higher (perforations, 0.07% to 0.72%; bleeding, 0.2% to 2.67%). Deaths occurred infrequently; reported rates ranged from 1 in 30 000 persons to 1 in 3000 persons. Mortality rates were higher in studies that included older patients and more symptomatic patients. The rate of screening-related death may be on the lower end of this range; one cost-effectiveness analysis estimated it to be 1 per 20 000 patients (29). Other clinically relevant complications were reported too infrequently and measured too inconsistently to allow accurate estimation of their true incidence.

DISCUSSION

Our systematic review supports the effectiveness of screening as a means of reducing death from colorectal cancer. For biennial FOBT, three high-quality randomized, controlled trials have shown disease-specific reductions in mortality rate of 15% to 21% over 8 to 13 years. Annual FOBT with rehydrated slides seems to be more effective in reducing mortality rates (33% in one trial). Case–control studies have shown that sigmoidoscopy and possibly colonoscopy are also associated with decreased death from colorectal cancer. The combined strategy of FOBT and sigmoidoscopy was supported by one nonrandomized trial that showed a borderline statistically significant reduction in mortality rates (43%) when FOBT was added to rigid sigmoidoscopy (4). This strategy was also supported by indirect evidence showing increased yield with both tests compared with FOBT alone. Double-contrast barium enema has not been studied as extensively as other screening methods; further data are required in screening populations.

Although strong direct and indirect evidence supports colorectal cancer screening, no trials have directly compared different screening strategies by using colorectal cancer incidence or mortality rates as the end point of interest. Some groups believe that recent evidence showing the superior single-test accuracy of colonoscopy proves its broader superiority and have recommended it as the procedure of choice for screening. However, these analyses have not always considered differences in yield over time, complications, and real-world performance, which may not always favor colonoscopy (62, 63). One solution to these problems would be to perform a trial of colonoscopy, but such a trial would be expensive, particularly if colonoscopy were compared with other screening methods rather than with no screening, and would require many years of follow-up. In the face of good general evidence supporting screening but uncertainty about the most effective screening method, providers and patients may benefit from discussing pros and cons and from incorporating patients' preferences into decisions about how to screen (64).

Several areas of colorectal cancer screening and prevention warrant additional research. There is a critical need to learn more about adherence to screening among informed patients. Furthermore, we need better data on the real-world complication rates of colonoscopic screening and polypectomy, including whether complications become more or less likely as procedure volume increases. Double-contrast barium enema should be studied in a screening population. The accuracy of novel screening techniques, including virtual colonoscopy and genetic stool tests (or other novel noninvasive tests), should be evaluated in screening populations.

Additional means of prevention, including chemopreventive agents (such as nonsteroidal anti-inflammatory drugs, calcium, or estrogen), also warrant further study. Behavioral factors, including physical activity, dietary fat intake, dietary fiber intake, and fruit and vegetable consumption, seem to be related to colorectal cancer incidence. Further research would clarify whether these relationships are causal or the result of uncontrolled confounding.

Despite its apparent effectiveness, colorectal cancer screening is currently underused by age-eligible adults because of patient-, provider-, and system-specific barriers (65). Effective colon cancer screening requires ongoing efforts to ensure test ordering and adherence. Screening with FOBT, for example, may require offering annual testing to 500 to 1000 people for 10 years to prevent one death from colorectal cancer (2). Although this level of effort may seem inefficient or low in yield, the potential benefit is large and the costs per person are small. To achieve high rates of screening in real-world settings rather than in trials, which focused strictly on one aspect of preventive care, colorectal cancer screening must be integrated with other care needs, including other preventive services.

Several strategies have been shown to be effective in raising screening rates in primary care settings over the short term, including reminder systems, patient decision aids, and special screening clinics (66). Further research is needed to determine whether such systems can maintain their effect over time and to identify novel means of reaching persons at risk who currently are not served or are underserved by the existing health care system.

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Current author addresses and the Appendix are available at www.annals.org.

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ON BEING A DOCTOR

Doctor's Luck

My father, Katsumi James Nakadate, who had known from the age of 4 that he would become a physician, retired from the practice of anesthesiology when he was 67. He retired from fishing a few years later, acknowledging a veteran's respect for fast-moving water and an intelligent fear of falling down one of the Oregon riverbanks where he had waved magic with a spinning rod for many years—on the Wilson, Trask, Nehalem, Nestucca, Deschutes. But he held on to his fishing vests until he was 85.

A tan vest for steelhead gear, rust brown for salmon, and khaki for trout. Always neatly packed and ready to go: snaps and swivels in tiny plastic envelopes, lures and flies, sinkers, hooks carefully snelled and coiled into plastic leader wallets, hook-sharpening stones, nail clippers to trim off nubs of extra line after knots were tied—and a hemostat, retired from surgical duty, for deftly extracting hooks from the mouths of conquered fish, many to be released.

In late fall and through the winter, he always welcomed the sudden grace of an open day or afternoon without surgery, another chance to put a line in the water. From June to September, off-season for the major runs of steelhead and salmon, he would occasionally drive over an hour from Portland to one of his favorite streams, just "to look at the river." Sometimes this meant that he simply needed the river's consolation when surgery didn't go well. But usually it meant, "I want to look the water over when it isn't there"—reduced to a creek-like flow with driftwood bleaching in the sun—to see how the spring runoff might have altered the architecture. Sometimes he took me with him.

Highway Hole. Coffee Can Hole. The Meadows. Familiar places that could be made unfamiliar by the rush of water, or flooding. He walked the glides and riffles, saw the secret shelves of the long, deep drifts and charted the mysterious holes where the biggest fish would lie. His memory charted runs and stumps and shallows, odd outcroppings of rock and fallen trees. When pebbly beds were merely walkways and silty sandbars absorbed the summer heat, he could spot the snags that would challenge him in January, with ice freezing in the guides of the rod, and when submerged secrets could tie up or steal his gear, robbing him of time, patience, concentration, and success.

Before hanging up a vest after a fishing trip, he checked and sharpened hooks, felt leaders and line for nicks and flaws, and made sure snaps and swivels would still bite and spin as if they had just come out of the box. Damaged gear was repaired or discarded and replaced. Reels exposed to tidewater were rinsed off, and rods were checked for injury or wear, from tips to ferules to butts. He had been an Eagle Scout, and his mantra was, "Be prepared." This was his protection against the sad litany of the failed sportsman and athlete—*coulda, woulda, shoulda.* He believed in his ability to meet the river on its own terms, but his faith, like Pasteur's, left nothing to chance.

At home, his habit was to disappear for an hour or two after supper—"however long it takes"—to make his evening rounds: to talk to patients a final time before the surgeries they would be having the next morning, to make a final check of their medical records and their state of mind.

He gave them last-minute pep talks and made sure he and the surgeon would not be taken unaware by some uncharted risk—an unmentioned allergy, a crucial bit of genetic information or medical history, an unnecessary fear or unspoken panic. He reminded the frightened or despairing why they were going through with the surgery at all—for spouse, children, grandchildren, their own worth and further potential as human beings. He told them what to expect in the operating room. And, of course, he made sure his equipment was ready for the moment when he would take them under and when, by compressing the drab, rubbery anesthesia bag with his right hand, he would have to breathe for the sleeping patient.

He fought the connivance of surprise and failure with motivation that was personal and a preparation that was long—his Boy Scout first aid training, his and his mentors' helplessness before his mother's kidney failure as he was about to receive his medical degree, his army surgeon's outrage at the rending of soldiers' lives in the frozen misery of the Bulge, listening at night (while I did my own homework) to conference papers on clumsy wheels of tape, lugged home with a bulky gray recorder from the hospital library.

He was a marvelous fisherman, but an even better doctor. When he finally had to give up his life's possessions, the fishing vests were the last to go. He never did relinquish the small black bag he had carried through internship, residency, and beyond, with the emergency medications, small scalpel, and stethoscope inside. He kept it on a bookshelf near his bed, scuffed at the corners and scratched a little on the sides, ready to take a blood pressure any time you asked.

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LETTERS

COMMENTS AND RESPONSES

Physicians and Joint Negotiations

TO THE EDITOR: The position paper on joint negotiations (1) and the accompanying editorial (2) consider the role of joint negotiations in maintaining physician autonomy. The Canadian experience may be of some interest.

In Canada, unlike in the United States, state governments are the sole providers of medical insurance, but like in the United States, physicians are in fee-for-service private practice. Government (socialized) medical insurance means a monopsonistic (single) payer. This is an apparently insurmountable obstacle to physician autonomy, especially when the monopsonist (the government) has the power to unilaterally determine "the terms and conditions of physician service," as the law stated when the system was started in Saskatchewan, Canada, in 1962.

Months of previous negotiations over this clause were fruitless, which led Saskatchewan physicians to withdraw all but emergency services (strike) on the implementation date. It took 23 days to reach an agreement that required the government to amend the law to meet our concerns, an end not reachable by negotiations alone. Striking tarnished our reputation outside the province but not inside—voters soundly trounced the governing political party in the general election a few months later. The strike was also prophylactic. There has never been a need for a repeat.

Doctors struck, but patients won. In return for 23 days of inconvenience, patients have had 39 years of care managed by physicians, not insurers. Patients' rights and physician autonomy are of the same coin.

This does not mean that all is well in Canadian Medicare. The system has warts (especially related to access time), but the strike fulgurated the threat to physician autonomy. Incidentally, Canadians have trouble understanding how the U.S. psyche can tolerate "managed care." It is the beatification of conflict of interest.

Although the Canadian insurance system covers 100% of the population and the insurance is physician managed, compared with 85% of the population insured and an insurer-managed system in the United States, Canadian health care (measured as a portion of the gross domestic product) is 30% cheaper. Some of this cost difference, however, probably comes from the deficiency in access time in the Canadian system.

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Blue Light and Milk

TO THE EDITOR: I am an enthusiastic reader of "On Being a Doctor," which is usually the first section I turn to in *Annals*. These essays have consistently described experiences and insights that were interesting, original, and thought provoking. My disappointment in the essay "Blue Light and Milk" (1) was therefore acute. This memoir struck me as sentimental and self-indulgent and the language as both trite and pretentious. I have no doubt that Dr. Morowitz is a warm, loving, and totally admirable father, but his reminiscences would have been more appropriate in a parenting magazine than in *Annals of Internal Medicine.*

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Fruit and Vegetable Intake and Coronary Heart Disease

TO THE EDITOR: Joshipura and colleagues (1) presented epidemiologic evidence suggesting that consumption of green leafy vegetables and vitamin C–rich fruits and vegetables protects against coronary artery disease. The cardioprotective effect of green leafy vegetables may be due to high levels of the antioxidant lutein. In a recent experiment using epidemiologic data, an in vitro model, and a mouse model, Dwyer and coworkers (2) showed that lutein, a carotenoid with no pro–vitamin A activity, protected against progression of arteriosclerosis. Lutein achieved this effect by lowering very low-density lipoprotein and intermediate-density lipoprotein levels via pathways that reduced inflammation and oxidative stress in the arterial wall. In a 1996 study comparing the plasma concentrations of antioxidant vitamins and carotenoids in two populations, Howard and associates (3) showed that lutein played a potential role in the prevention of coronary disease. In that study, the major difference in antioxidant status between the two populations was in the plasma concentration of lutein, which was approximately twofold higher in the population with lower incidence of coronary disease. Increased intake of green leafy vegetables also protects against age-related macular degeneration, the leading cause of irreversible blindness in persons older than 65 years of age in developed countries (4). Since arteriosclerosis is a risk factor for age-related macular degeneration, the widely recognized role of lutein in the prevention of the latter disorder must be at least partially related to its prevention of arteriosclerosis.

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TO THE EDITOR: We read with interest the study by Joshipura and colleagues (1), which reported that the consumption of one additional daily serving of fruit or vegetables (beyond the median level of consumption) was associated with a 4% reduction in coronary events. Relative terms often do not give a good sense of the benefit of interventions. Increasingly, there is a call for the use of absolute numbers, such as the number needed to treat for benefit (NNT_B), as a way of addressing the "clinical bottom line" when interpreting the results of clinical studies (2). In applying this concept to the study by Joshipura and colleagues, we recognized that the NNT_B may not adequately convey the magnitude of the behavioral change required to prevent one event. As an alternative, we propose a new term, the ***number needed to eat for benefit***, or NNE_B.

We calculate the NNE_B in the following manner: In the Nurses' Health Study (3), the annualized rate of coronary events was 0.096% (1127 events in 84 251 women over 14 years). A 4% reduction in this rate would yield an absolute risk reduction of 0.004%, which can be translated into a NNT_B of 25 000 (that is, 25 000 women like the women in this study would need to eat an extra daily portion of fruit or vegetables to prevent one coronary event over 1 year). Multiplying the NNT_B over 1 year by 365 portions per year gives us a NNE_B of 9 125 000. In other words, the women in this study would need to consume 9 125 000 more portions of fruit or vegetables to prevent a single coronary event. We estimate that the NNE_B for the men in the Health Professionals' Follow-Up Study (4) would be 2 807 580 portions.

The NNE_B may be a useful measure for giving practitioners and patients a better sense of the impact of dietary changes. We suggest that authors consider using it in reports on the association between diet and clinical outcomes.

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IN RESPONSE: The suggestion by Drs. Alves-Rodrigues and Thomas that the cardioprotective effect of green leafy vegetables may be related to high lutein levels is based on an animal study of lutein and arteriosclerosis (1) and a study among humans examining the relation between lutein and other antioxidants and coronary disease (2). In our study, we mentioned that antioxidant vitamins, folate, fiber, and such minerals as potassium may contribute to the apparent beneficial effects of fruits and vegetables, and we agree that lutein may also partly explain this benefit.

Dr. Lindenauer and colleagues propose a new term, NNE_B, as a better alternative to relative risk or to NNT_B. We estimated that for one person in our study sample to avoid a coronary event, 1443 persons would have to increase consumption of fruits and vegetables by one serving per day for 12 years. Lindenauer and colleagues suggest that the NNT_B may not adequately convey the magnitude of the behavioral change required to prevent one event. However, the NNE_B is more difficult to interpret because it does not include information on number of participants and time. Also, as we mentioned in our study, any estimates like these are largely dependent on characteristics of the study sample and can be very misleading (for example, they could easily vary 50-fold depending on age distribution). Furthermore, it is important to differentiate between implications for drug trials and implications for fruits and vegetables, which are unlikely to have side effects and are beneficial for many diseases.

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Questioning the Treatment of Venous Thromboembolism

TO THE EDITOR: In their review of clinical trials that have influenced the treatment of venous thromboembolism (1), Drs. Hirsh and Bates omitted a crucial study by Nielsen and colleagues (2). The Nielsen study compared anticoagulation with heparin plus phenprocoumon and therapy with phenylbutazone in patients with deep venous thrombosis (DVT). The results of the study were negative: One of 48 patients who received anticoagulants and 0 of 42 patients who received phenylbutazone died of pulmonary embolism. The only other previously published randomized, controlled trials of anticoagulants versus placebo in DVT also showed no benefit with anticoagulation (3, 4).

Heparin and vitamin K antagonists became standard treatment for DVT and pulmonary embolism in the 1940s, before randomized, controlled trials were routinely used to prove efficacy. The U.S. Food and Drug Administration (FDA) allowed these therapies to be "grandfathered in" in the early 1960s, when proof of efficacy became required for FDA approval. Low-molecular-weight heparins have been granted indications for treatment of DVT because randomized, controlled trials have shown their effects to be equivalent to those of heparin in trials that did not use "unanticoagulated" controls.

Drs. Hirsh and Bates referenced a randomized trial by Barritt and Jordan (5) comparing anticoagulants with placebo in patients with pulmonary embolism. That trial should not be used as a basis for medical treatment policy. Its flaws include a small number of patients ($n = 35$), clinical diagnosis without lung scans or angiograms, 10 days of prescribed complete bed rest, and questionable determinations of deaths from pulmonary embolism.

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IN RESPONSE: Our article discussed clinical trials that have influenced practice. The study by Barritt and Jordan (1) did so and was of historical importance. Barritt and Jordan found that in patients who were considered to have pulmonary embolism, 5 of 19 who did not receive anticoagulants died compared with 0 of 16 who did. This difference was statistically significant ($P = 0.036$). Several subsequent randomized trials (2–4) have supported Barritt and Jordan's contention that anticoagulants are indicated to treat patients with venous thromboembolism.

The study by Nielsen and colleagues (5) is interesting but did not influence practice. The authors themselves stated, "[T]he patient population. . . is relatively small with wide confidence intervals for differences between groups. Before more general recommendations can be made, a large-scale placebo-controlled study is needed to evaluate the possible effect of [anticoagulant] treatment in DVT patients who can be mobilized from the first day." It should also be noted that the relative risk for progression of proximal venous thrombosis in this study was almost 40% greater in phenylbutazone-treated patients than in anticoagulant-treated patients.

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RESEARCH LETTERS

Rapid-Onset Type 1 Diabetes Mellitus without Pancreatic Exocrine Dysfunction

TO THE EDITOR: Imagawa and coworkers (1, 2) proposed a nonautoimmune fulminant subtype of type 1 diabetes mellitus characterized by the absence of insulitis and diabetes-related antibodies, rapid-onset elevated levels of serum pancreatic enzyme at diagnosis, and lymphocytic infiltration of the exocrine pancreas. However, pancreatic exocrine dysfunction may suggest an autoimmune rather than a nonautoimmune response in this subtype (3, 4).

We examined the pancreatic biopsy specimen of a 50-year-old Japanese man with rapid-onset type 1 diabetes mellitus. He was admitted to our hospital with diabetic ketoacidosis 3 days after rapid-onset symptoms of hyperglycemia. His blood glucose concentration was 26.3 mmol/L (474 mg/dL), and his glycosylated hemoglobin level was 0.061 (6.1%). Six days before admission, these values had been 3.9 mmol/L (70 mg/dL) and 0.054 (5.4%), respectively. Serum pancreatic enzyme levels were normal, and there were no diabetes-related antibodies. The patient's *HLA-DRB1*, *DQA1*, and *DQB1* genotypes were *0405/*0410, *0303/*0303, and *0401/*0402. No significantly elevated titers of antiviral antibodies, including rotavirus, were detected.

Histopathologic examination of a biopsy specimen obtained at the 33rd day after the patient's admission showed absence of insulitis and cell infiltration in the exocrine pancreas (Figure, *panels A and B*). The islets contained a majority of α-cells and a minor population of Δ-cells, but no β-cells (Figure, *panels C through E*). No CD3$^+$ T lymphocytes were evident in the islets and the exocrine pancreas (Figure, *panel F*).

Although our patient is very similar to the patients described by Imagawa and colleagues (1, 2), he did not have pancreatic exocrine dysfunction. Therefore, we believe that no autoimmune response was involved in the pathogenesis and that our case might be classified as unadulterated nonautoimmune fulminant type 1 diabetes mellitus rather than as a variant form of the subtype proposed by Imagawa and colleagues (1, 2).

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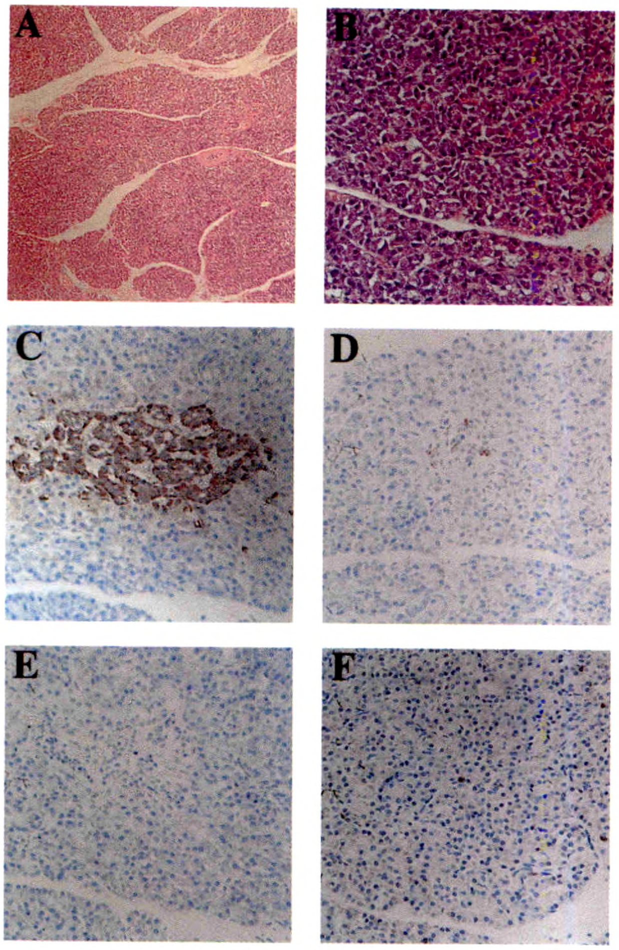
Figure. Serial sections of the pancreas.



A and B. The islets of Langerhans and any signs of inflammation, including insulitis, edema, necrosis, hyalinization, and cell infiltration to the exocrine pancreas, are not manifested by light microscopy (hematoxylin–eosin; original magnification, ×100 [*panel A*] and ×400 [*panel B*]). **C through E.** The islet containing a majority of α-cells (antiglucagon antibody [*panel C*]; original magnification, ×400) and a minor population of Δ-cells (antisomatostatin antibody [*panel D*]; original magnification, ×400) but no β-cells (anti-insulin antibody [*panel E*]; original magnification, ×400) is evidenced by immunohistochemical studies using the standard avidin–biotin immunoperoxidase technique. **F.** No $CD3^+$ T lymphocytes are observed both in the islets and the exocrine pancreatic tissue (anti-$CD3^+$ T lymphocytes antibody; original magnification, ×400).

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Hepatotoxicity after Prophylaxis with a Nevirapine-Containing Antiretroviral Regimen

TO THE EDITOR: Postexposure prophylaxis is recommended after high-risk occupational HIV exposure in health care workers (1). Some regimens include non-nucleoside reverse transcriptase inhibitors because these agents have favorable pharmacokinetics and dosing schedules and have successfully prevented mother-to-child HIV transmission (2). The use of nevirapine, a non-nucleoside reverse transcriptase inhibitor, is complicated by 1% rates of hepatotoxicity and the Stephens–Johnson syndrome in HIV-infected persons (3). Nevirapine-associated hepatotoxicity has been noted in 8 of 41 healthy volunteers in phase I trials and in 5 of 41 sexual partners of HIV-infected persons who received postexposure prophylaxis that contained nevirapine (4). Fortunately, in all cases, toxicity resolved after nevirapine was withdrawn.

Because of concern that similar toxicity may have occurred elsewhere and uncertainty that other hepatotoxins may complicate findings from sexual contacts of HIV-infected persons, we evaluated use of nevirapine-containing postexposure prophylaxis after occupational HIV exposures. Three hospitals and one outpatient clinic in the Chicago area used nevirapine-containing regimens as second-line postexposure prophylaxis from October 1999 to September 2000. Among 174 health care workers who received postexposure prophylaxis, 8 received nevirapine-containing regimens and 5 developed severe hepatotoxicity (**Table**). A liver biopsy from health care worker 1 showed centrilobular fibrosis and minimal mixed portal infiltrates containing eosinophils. Hepatotoxicity resolved after corticosteroid administration. Health care worker 4, who had fulminant hepatic necrosis, received a liver transplant. At follow-up, none of the health care workers had evidence of HIV infection or hepatitis B or C virus infection.

Nevirapine-associated hepatotoxicity may represent a hypersensitivity reaction also characterized by skin rashes, fevers, and peripheral eosinophilia; rapid onset; and absence of mitochondrial toxicity characteristic of nucleoside analogue toxicity in pathologic specimens. Although nevirapine is potentially useful for postexposure prophylaxis, our findings suggest that immunocompetent persons may be at risk for nevirapine-associated hepatotoxicity that may not be rapidly reversible or may progress to fulminant hepatic necrosis. The use of postexposure prophylaxis regimens containing nevirapine should be discouraged.

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Table. **Cases of Hepatitis in Five Health Care Workers in One Midwestern City Who Received a Postexposure Prophylaxis Regimen Consisting of Zidovudine and Lamivudine, 150 mg Twice Daily, and Nevirapine***

Variable	Health Care Worker 1	Health Care Worker 2	Health Care Worker 3	Health Care Worker 4	Health Care Worker 5
Profession	Physician	Nurse	Nurse	Phlebotomist	Nurse
HIV exposure	Fluid splash	Saliva splash	Needlestick	Needlestick	Needlestick
Age, *y*	38	39	33	43	47
Sex	Male	Female	Female	Female	Female
Day of onset	21	16	8	14	12
Length of PEP, *d*	21	20	25	20	22
Time receiving nevirapine, 200 mg/d, *d*	14	14	8	14	12
Time receiving nevirapine, 200 mg twice daily dose, *d*	7	2	0	0	0
Duration of symptoms, *d*	60	18	21	20	42
Skin rash > 50% of body?	No	No	Yes	No	Yes
Temperature > 101° F?	No	No	Yes	Yes	Yes
Peak ALT level, U/L	–	248	215	1080	298
Peak AST level, U/L	97	356	117	2370	307
Peak total bilirubin level, mg/dL	34.0	6.7	0.7	1.3	4.8
Peripheral eosinophilia?	No	Yes	Yes	No	Yes
Treatment (other than discontinuation of nevirapine)	Prednisone, 20 mg twice daily, for 60 days	None	Prednisone, 20 mg/d, for 5 days; rash and fever recurred 2 days later and prednisone therapy was re-initiated (20 mg/d for 2 wk)	Liver transplant	None

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; PEP = postexposure prophylaxis.

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CORRECTION

Correction: The Reliability of Medical Record Review for Estimating Adverse Event Rates

In a recent Brief Communication (1), the name of the second author, Stuart R. Lipsitz, PhD, was omitted from the byline. The byline should read "Eric J. Thomas, MD, MPH; Stuart R. Lipsitz, PhD; David M. Studdert, LLB, ScD, MPH; and Troyen A. Brennan, MD, JD, MPH."

Reference

1. Thomas EJ, Lipsitz SR, Studdert DM, Brennan TA. The reliability of medical record review for estimating adverse event rates. Ann Intern Med. 2002;136:812-6. [PMID: 12044129]

MEDICAL WRITINGS

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. Order phone numbers and Web sites can be used to place orders directly with publishers.

This Side of Doctoring: Reflections from Women in Medicine

Chin EL, ed. 424 pages. Thousand Oaks, CA: Sage Publications; 2002. $29.95. ISBN 0761923543. Order phone 800-818-7243.

Field of medicine: Medical education and professional development.

Format: Hardcover book.

Audience: Medical educators and trainees, physicians and their families, and friends and patients.

Purpose: To capture the essence of being a woman physician through largely autobiographical reflections on doctoring and sketches of doctors' personal lives.

Content: The book is an anthology of heartfelt and honest essays, stories, and poems written by more than 150 women (and a few men), edited by an academic general internist and mother on temporary leave from her medical career. The first chapter recounts the history of women in medicine, beginning with Harriet Hunt and Elizabeth Blackwell. The next chapter anthologizes essays and poems of "early pioneers," women who received their medical degrees between the 1850s and 1950s. Subsequent chapter topics follow the chronology of medical training and additional issues, such as mothering, barriers to career success, and family members' perspectives.

Highlights: What a delight to discover so many talented, skilled physician authors! The writing is nuanced, the emotions are genuine, and the delivery is candid. Readers will enjoy discovering works of contributors Sayantani DasGupta, Alison Moll, Danielle Ofri, Audrey Shafer, and others whose body of literature demands attention and celebration. The authors voice multiple aspects of the transition from layperson to physician. The parallels between being a patient and being a physician—feelings of loneliness, expressions of dismay over unmet personal needs—are striking and ironic. Tales of courage and conviction abound.

Limitations: The anthology format does not lend itself readily to deep exploration of an issue, construction of an argument, or counterpoint of an opposing perspective. However, the book does not purport to be anything other than a rich-textured assemblage of voices. Nevertheless, this compendium repeatedly documents persistent double standards and expectations for women physicians compared with their male counterparts—despite all the progress since 1850. Readers may wish the contributors had also applied their considerable insight and intellect to creating models of reform.

Comment: To experience this book is to relive the emotions from one's own medical training. It may inspire readers to write about their own experiences of medical life.

Reviewer: Catherine V. Caldicott, MD, Center for Bioethics and Humanities, State University of New York Upstate Medical University, Syracuse, New York.

Medical Humanities

Evans M, Finlay IG, eds. 292 pages. London: BMJ; 2001. $39.95. ISBN 0727916106. Order at www.bmjbooks.com.

Field of medicine: Humanities and medicine, medical ethics, and narrative medicine.

Format: Softcover book.

Audience: Physicians, bioethicists, humanities scholars who work in medical settings, specialists in patients' experiences of illness and the doctor–patient relationship, and students in health professions.

Purpose: To articulate the goals, justification, conceptual frameworks, and practice of medical humanities as it has developed in the United Kingdom.

Content: Sixteen essays divided into sections devoted to philosophical, pedagogic, and clinical dimensions of humanities and medicine. The authors include U.K. primary care physicians, literary scholars, philosophers, historians, artists, and writers involved in medical practice and medical education. The reader receives a robust and eclectic picture of ways in which British medicine is being fortified and changed by knowledge from and habits of the humanities. The field of medical humanities is conceptualized as a contributor to the education of health professionals, a set of methods for examining and critiquing medical science, and a source of therapeutic interventions in the care of individual patients.

Highlights: Essays by leaders in the field—including Martyn Evans, Robin Downie, Jane Macnaughton, and Ilora Finlay—examine the boundaries between medicine and the humanities and speak for the urgency of incorporating narrative knowledge and creative activities in the ordinary practice of medicine. The editors offer clear and insightful overarching summary material. Medical humanities in the United Kingdom differs fundamentally from the field in the United States; the book distinguishes the more empirical practice in the United Kingdom from a more theoretically driven practice in the United States and challenges the U.S. field to articulate its own goals and methods.

Limitations: Essays are uneven in quality and are related fragmentarily to one another.

Related readings: Greenhalgh and Hurwitz's *Narrative Based Medicine: Dialogue and Discourse in Clinical Practice* (BMJ, 1998) provides essays examining the clinical uses of narrative knowledge, also from the British perspective. For some aspects of such practices in the United States, see Anderson and MacCurdy's *Writing and Healing: Toward an Informed Practice* (National Council of Teachers of English, 2000) and Hunter's *Doctors' Stories: The Narrative Structure of Medical Knowledge* (Princeton Univ Pr, 1993).

Reviewer: Rita Charon, MD, PhD, College of Physicians and Surgeons of Columbia University, New York, New York.

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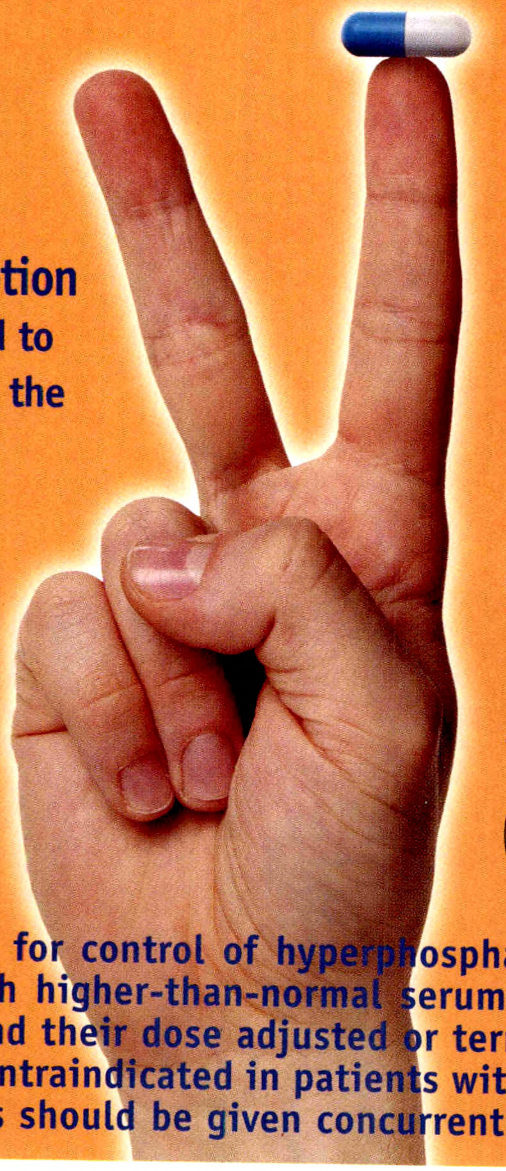

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References: 1. Sheikh MS, Maguire JA, Emmett M, et al. Reduction of dietary phosphorus absorption by phosphorus binders. *J Clin Inves.* 1989;83:66-73.
2. Mai ML, Emmett M, Sheikh MS, et al. Calcium acetate, an effective phosphorus binder in patients with renal failure. *Kidney Int.* 1989:36:690-695.

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New York Internal Medicine Board Review Course. New York, NY. Location: The Waldorf=Astoria Hotel. Director: Michael S. Niederman, MD, FACP. Groups A and D, $685; Group B, $485; Group C, $965. Course Code PG0206.

JULY 15-19, 2002

Washington, D.C. Internal Medicine Board Review Course. Washington, D.C. Location: Georgetown University Conference Center. Co-Directors: Margot G. Wheeler, MD, ACP–ASIM Member and Princy N. Kumar, MD, ACP–ASIM Member. Groups A and D, $825; Group B, $575; Group C, $1175. Course Code PG0207.

JULY 16-20, 2002

Seattle Internal Medicine Board Review Course. Seattle, WA. Location: Sheraton Seattle Hotel and Towers. Director: Douglas S. Paauw, MD, FACP. Co-Director: Joyce E. Wipf, MD, ACP–ASIM Member. Groups A and D, $825; Group B, $575; Group C, $1175. Course Code PG0208.

SEPTEMBER 26-28, 2002

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OCTOBER 3-5, 2002

Preparation for Recertification. San Diego, CA. Location: Marriott Mission Valley. Director: Douglas S. Paauw, MD, FACP. Groups A and D, $530; Group B, $395; Group C, $725. Course Code PG0210.

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Canadian Society of Internal Medicine Annual Scientific Meeting. To be held at The Westin, Halifax, NS. Dalhousie University Continuing Medical Education designates this program for Category 1 credit and certification by the Royal College of Physicians and Surgeons of Canada. Information: CSIM Secretariat, 774 Echo Drive, Ottawa, ON K1S 5N8; 613-730-6244; fax 613-730-1116; E-mail: csim@rcpsc.edu or www. csim.medical.org.

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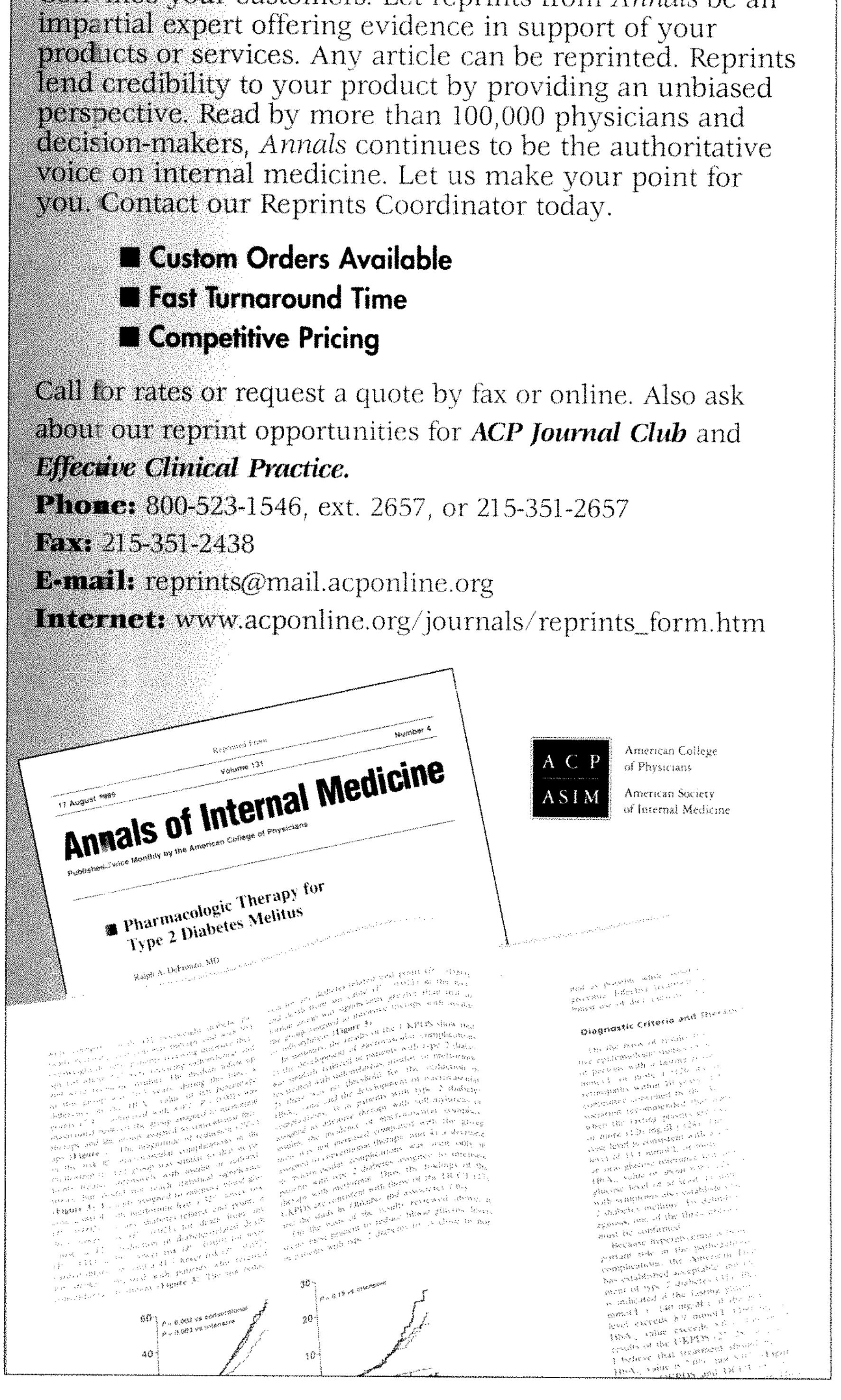

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Pharmacologic Therapy for Type 2 Diabetes Melitus
Ralph A. DeFronzo, MD

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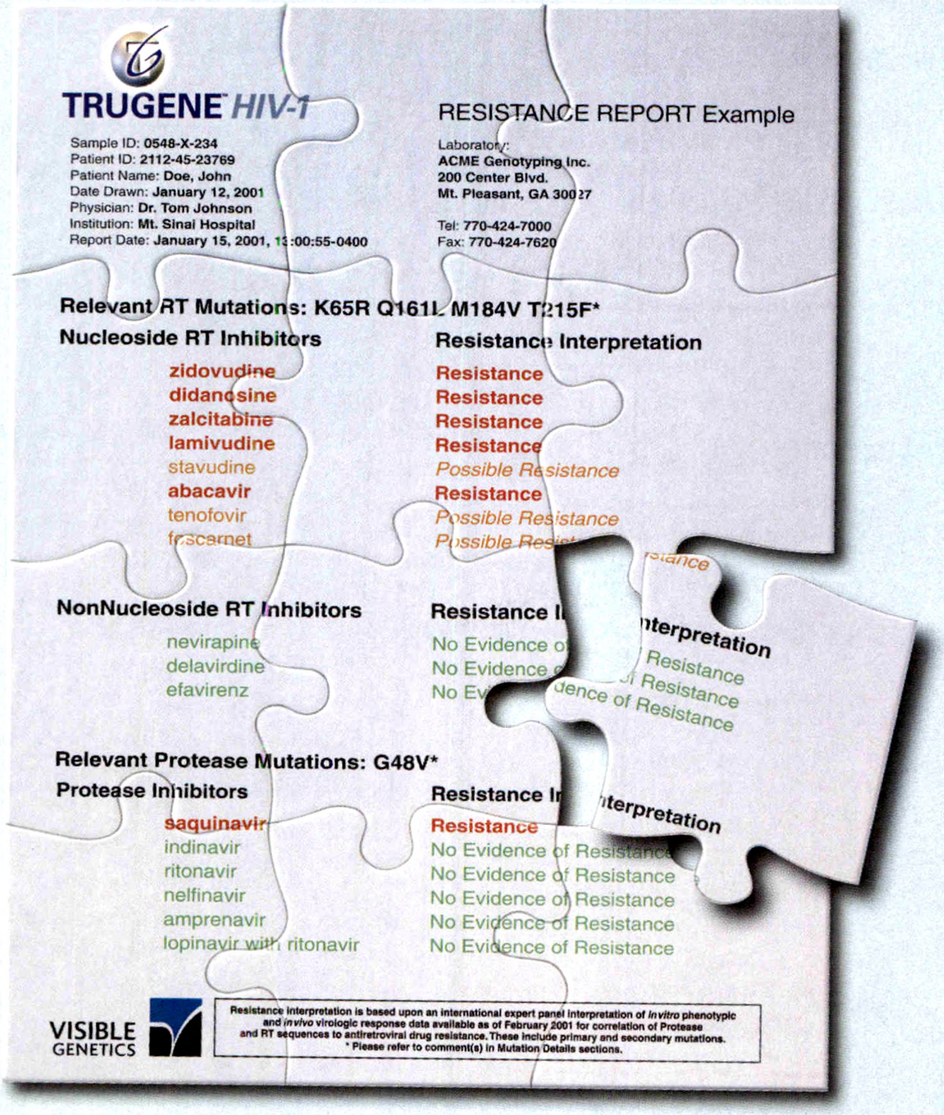

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Sample ID: **0548-X-234**
Patient ID: **2112-45-23769**
Patient Name: **Doe, John**
Date Drawn: **January 12, 2001**
Physician: **Dr. Tom Johnson**
Institution: **Mt. Sinai Hospital**
Report Date: **January 15, 2001, 13:00:55-0400**

Laboratory:
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200 Center Blvd.
Mt. Pleasant, GA 30027

Tel: **770-424-7000**
Fax: **770-424-7620**

Relevant RT Mutations: K65R Q161L M184V T215F*

Nucleoside RT Inhibitors	Resistance Interpretation
zidovudine	**Resistance**
didanosine	**Resistance**
zalcitabine	**Resistance**
lamivudine	**Resistance**
stavudine	*Possible Resistance*
abacavir	**Resistance**
tenofovir	*Possible Resistance*
foscarnet	*Possible Resistance*

NonNucleoside RT Inhibitors	Resistance Interpretation
nevirapine	No Evidence of Resistance
delavirdine	No Evidence of Resistance
efavirenz	No Evidence of Resistance

Relevant Protease Mutations: G48V*

Protease Inhibitors	Resistance Interpretation
saquinavir	**Resistance**
indinavir	No Evidence of Resistance
ritonavir	No Evidence of Resistance
nelfinavir	No Evidence of Resistance
amprenavir	No Evidence of Resistance
lopinavir with ritonavir	No Evidence of Resistance

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* Please refer to comment(s) in Mutation Details sections.

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References: 1. TRUGENE™ *HIV-1* Genotyping Kit Product Insert. 2. Lee S, Griswold M, Shaker-Irwin L et al. Reproducibility, precision and turn-around-times of results generated by laboratory-developed "home-brew" genotypic drug resistance assays vary dramatically when compared to results generated by a kit-based genotyping assay. Presented at 17th Annual Clinical Virology Symposium, Clearwater, April 2001. 3. Day S, Hough L, Huong J et al. Reproducibility of results generated by a kit-based HIV-1 genotypic drug resistance assay demonstrated when compared to laboratory-developed "home-brew" genotypic and phenotypic assays offered through reference laboratories. Presented at the United States Conference on AIDS, Atlanta, October, 2000. 4. Information taken from www.medscape.com: Medscape HIV/AIDS: a) Annual update 2000 – resistance assays and b) Human immunodeficiency virus drug resistance testing: state of the art in genotypic and phenotypic testing of antiretrovirals. *Pharmacotherapy* © 2000.

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Annals of Internal Medicine

SUMMARIES FOR PATIENTS

Treatment of Histoplasmosis in Patients with HIV Infection

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Safety and Efficacy of Liposomal Amphotericin B Compared with Conventional Amphotericin B for Induction Therapy of Histoplasmosis in Patients with AIDS." It is in the 16 July 2002 issue of *Annals of Internal Medicine* (volume 137, pages 105-109). The authors are PC Johnson, LJ Wheat, GA Cloud, M Goldman, D Lancaster, DM Bamberger, WG Powderly, R Hafner, CA Kauffman, and WE Dismukes, for the U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group.

What is the problem and what is known about it so far?

People who are infected with human immunodeficiency virus (HIV) have weak immune systems and cannot fight infections well. Sometimes, they get serious infections with fungi. The fungal infections can spread throughout the body and can be fatal. Successful treatment requires taking powerful antifungal drugs for long periods (weeks to months).

Histoplasmosis is a serious fungal infection that occurs in as many as 5% to 20% of people with HIV infection. The standard initial treatment for severe histoplasmosis is a drug called *amphotericin B*. Amphotericin B is usually given daily, through a vein, for a few weeks. Later, a different antifungal drug that can be taken by mouth is given for several months. Many side effects, such as fever, chills, nausea, and problems with kidney function, can occur with standard preparations of amphotericin B. New preparations of amphotericin B that do not have as many side effects are needed.

Why did the researchers do this particular study?

To compare the efficacy and safety of two different preparations of amphotericin B for treating severe histoplasmosis in adults with HIV infection.

Who was studied?

81 adults with HIV infection and histoplasmosis that had spread (disseminated) throughout the body.

How was the study done?

Patients were randomly assigned to receive either a standard preparation of amphotericin B or a special preparation called *liposomal amphotericin B*. Both preparations were given through a vein over a period of 2 hours each day for several days (1 to 2 weeks). Neither the patients nor their doctors knew which preparation was given. Patients who improved were switched to an antifungal drug (itraconozole) that was given by mouth. Treatment response was defined as no fever for at least 3 days; no worsening of any symptoms, physical findings, or laboratory test results; and improvement in at least one symptom or finding related to histoplasmosis. After 3 months of follow-up, the researchers compared treatment responses and side effects in patients given standard amphotericin B and those given liposomal amphotericin B.

What did the researchers find?

Patients given liposomal amphotericin B responded to treatment more often than those given standard amphotericin B (88% vs. 64%). Fewer patients given liposomal amphotericin died (2% vs. 13%). Only 25% of the patients who were given liposomal amphotericin B had side effects; 63% of the patients given the standard preparation had side effects. Fewer patients who received liposomal amphotericin had problems with kidney function (9%) than those given the standard preparation (37%).

What were the limitations of the study?

Both preparations were given into the veins over a 2-hour period. Either preparation given more slowly and continuously over a 24-hour period might work better and cause fewer side effects.

What are the implications of the study?

Although expensive, liposomal amphotericin B is better than standard amphotericin B for treating disseminated histoplasmosis in patients with HIV infection.

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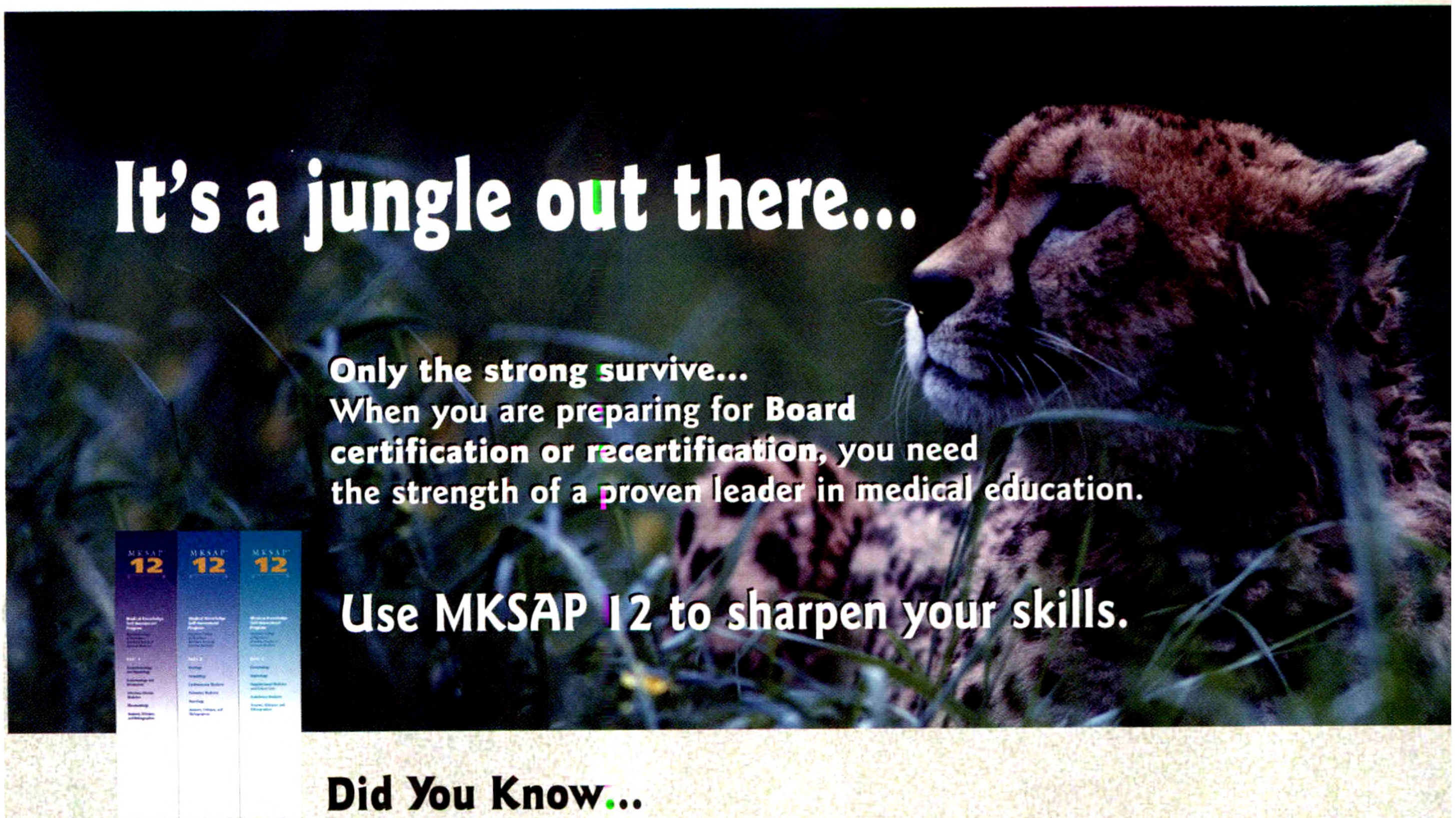
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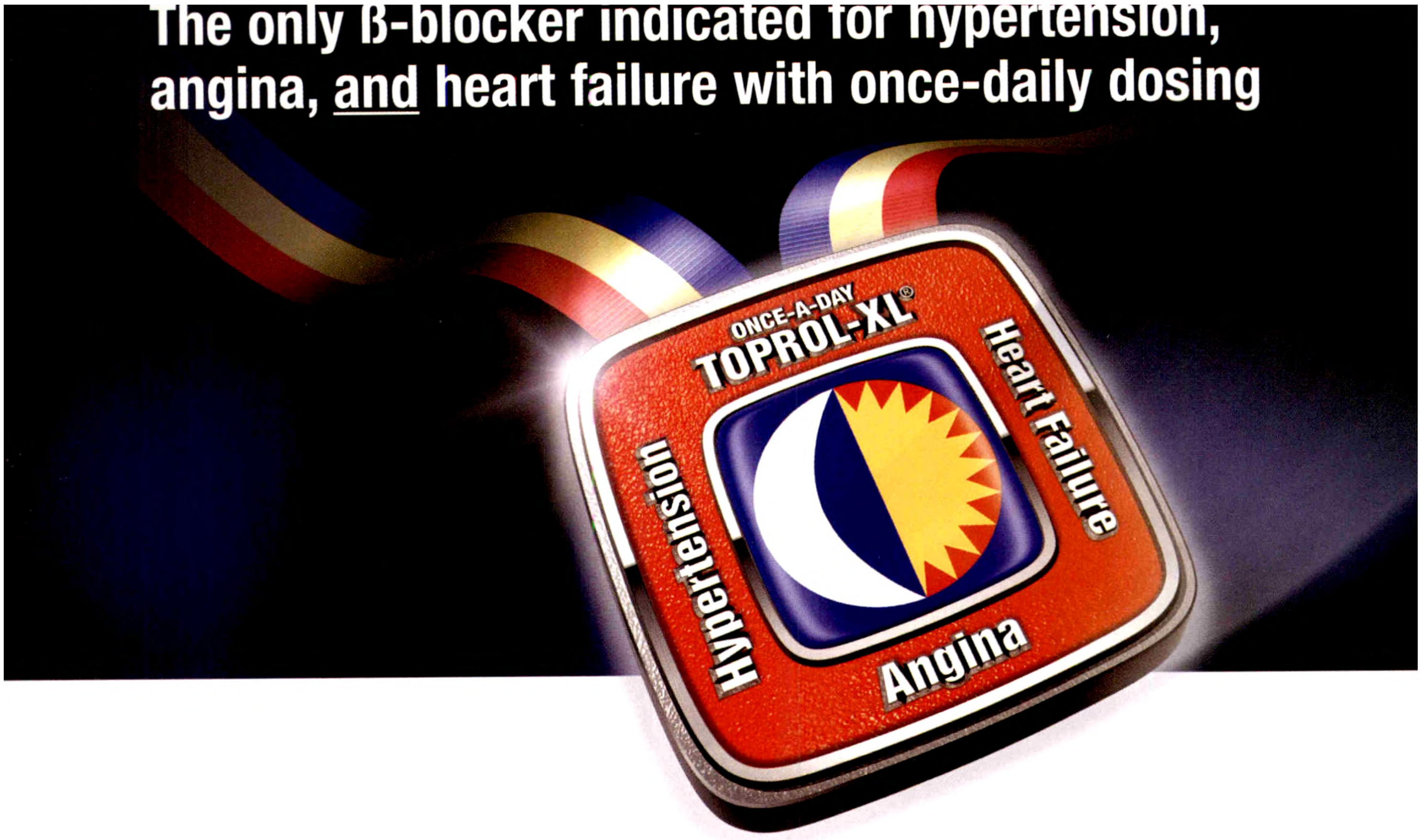

- TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents
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- TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place)

> Patients taking TOPROL-XL should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. The dosage should be reduced gradually over a 1- to 2-week period, and the patient should be carefully monitored.

Please see brief summary of full Prescribing Information, including full boxed WARNING, on adjacent page.

www.toprol-xl.com

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extended-release tablets

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50 mg
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INDICATIONS AND USAGE Hypertension: Toprol-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. **Angina Pectoris:** Toprol-XL is indicated in the long-term treatment of angina pectoris. **Heart Failure:** Toprol-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, Toprol-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

CONTRAINDICATIONS Toprol-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS).

WARNINGS

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol-XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol-XL should be used (see DOSAGE AND ADMINISTRATION). ***Major Surgery:*** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Toprol-XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers. ***Diabetes and Hypoglycemia:*** Toprol-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. ***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS General: Toprol-XL should be used with caution in patients with impaired hepatic function. Worsening cardiac failure may occur during up-titration of Toprol-XL. If such symptoms occur, diuretics should be increased and the dose of Toprol-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of Toprol-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Toprol-XL. **Information for Patients:** Patients should be advised to take Toprol-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue Toprol-XL without consulting the physician. Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol-XL. Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath. **Laboratory Tests:** Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase. **Drug Interactions:** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg, tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. **Pregnancy Category C:** Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol-XL is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Clinical studies of Toprol-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients. Of the 1,990 patients with heart failure randomized to Toprol-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Risk of Anaphylactic Reactions:** While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS Hypertension and Angina: Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate. ***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported. ***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS). ***Respiratory:*** Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS). ***Gastrointestinal:*** Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients. ***Hypersensitive Reactions:*** Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported. ***Miscellaneous:*** Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol. **Potential Adverse Reactions:** A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol-XL. ***Central Nervous System:*** Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Hematologic:*** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. ***Hypersensitive Reactions:*** Fever combined with aching and sore throat, laryngospasm, and respiratory distress. **Heart Failure:** In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing Toprol-XL in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of Toprol-XL patients discontinued for adverse events vs. 12.2% of placebo patients. The table below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the Toprol-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Events Occurring in the MERIT-HF Study at an Incidence ≥ 1% in the Toprol-XL Group and Greater Than Placebo by More Than 0.5%

	Toprol-XL N=1990 % of patients	Placebo N=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Other adverse events with an incidence of > 1% on Toprol-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue. **Post-Marketing Experience:** The following adverse reactions have been reported in post-marketing use: *Gastrointestinal:* hepatitis; *Musculoskeletal:* arthralgia.

OVERDOSAGE Acute Toxicity: There have been a few reports of overdosage with Toprol-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol-XL. **Signs and Symptoms:** Overdosage of Toprol-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis. **Treatment:** In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed: ***Elimination of the Drug:*** Gastric lavage should be performed. ***Bradycardia:*** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. ***Hypotension:*** A vasopressor should be administered, e.g., levarterenol or dopamine. ***Bronchospasm:*** A beta$_2$-stimulating agent and/or a theophylline derivative should be administered. ***Cardiac Failure:*** A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION Toprol-XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol-XL, the same total daily dose of Toprol-XL should be used. As with immediate release metoprolol, dosages of Toprol-XL should be individualized and titration may be needed in some patients. Toprol-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed. **Hypertension:** The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied. **Angina Pectoris:** The dosage of Toprol-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1–2 weeks (see WARNINGS). **Heart Failure:** Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Toprol-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of Toprol-XL is 25 mg once daily for two weeks in patients with NYHA class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of Toprol-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of Toprol-XL or temporarily discontinue it. The dose of Toprol-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce Toprol-XL. If heart failure patients experience symptomatic bradycardia, the dose of Toprol-XL should be reduced.

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Internal Medicine and Primary Care

California

Northern California. Full spectrum general internal medicine group requires fifth BC/BE internist. State of the art medical center. Strong specialty support and good call coverage. Competitive income, benefits package, malpractice insurance and moving expenses. Beautiful surroundings without urban problems and congestion. Worldclass sports and recreation. Send CV in confidence or call: Sharon Mac Kenzie 800-735-4431 Fax: 707-824-0146 e-mail: mackenz@sonic.net.
W-IN2N.411.TF

California Coast. Enjoy a better quality of life. Experienced BC internist. San Luis Obispo. Busy group practice adjacent to hospital. Replace departing MD. Fax CV 805-541-4236.
W-IN2N.434.2X

BC-BE Internist in Bay Area: Position available for thriving IM-FP in East Bay Area. First year salary guaranteed. Reasonable buy-in to become full partner. Fax CV to: Jeffrey Frank, MD at 510-237-9685. No Visas.
W-IN2N.429.1X

General Internal Medicine - San Diego, California. Scripps Clinic Medical Group, Inc., in San Diego has full-time employment opportunities available for Internists. Requires California Medical License and BC. Send CV to: 10666 N. Torrey Pines Road, Mail Drop MS129, La Jolla, CA 92037; or e-mail: jmulvey@scrippsclinic.com. EOE.
W-IN2N.428.1X

San Francisco/Bay Area. Marin County is on of the most desirable areas in the country. Join a single-specialty group of Board-certified internists. Call 1:8. Phenomenal office setting. Enjoy the quality of life only the greater Bay Area can offer. Contact Pam Kinsella at 800-851-8805, x3423; fax 314-726-0026; e-mail: pkinsella@cejka.com. ID#21431A. For more opportunities, visit www.cejka.com.
W-IN2N.388.2X

Outstanding Internal Medicine opportunities in Northern California, Sacramento for BC-BE internist to join Sutter Medical Group, a prestigious multispecialty medical group linked to Sutter Health and ranked among the nation's top 15 integrated healthcare networks. CV to Sutter Health Physician recruitment; e-mail: wadhwas@sutterhealth.org mailto:wadhwas@sutterhealth.org Web site: www.go.sutterhealth.org.
W-IN2N.369.3X

Colorado

Denver-IM group. $125,000 base. 1-year partnership. 4-day workweek. Partners average $250,000. Contact Dr. Warren Graboyes Tel: 970-476-0901; Fax: 970-476-0839; E-mail: Warren@central-res.com.
W-IN2N.435.2X

District of Columbia

The Department of Medicine, Division of General Internal Medicine at the George Washington University faculty associates, an independent non-profit clinical practice group affiliated with The George Washington University, is seeking a clinician-educator General Internist. the faulty member will be involved in clinical teaching programs and an active clinical practice. The successful candidate should have a strong interest in teaching, clinical research and clinical practice. Academic rank at The George Washington University will be commensurate with experience. Board certification/eligibility in internal medicine is required. Review of applications is ongoing and will continue until the position is filled. Send CV to Alan G. Wasserman, MD, Chairman, Department of Medicine, c/o Christy Dugan, 2150 Pennsylvania Avenue, NW, Suite 5-411, Washington, DC 20037, or e-mail to cdugan@mfa.gwu.edu. The George Washington University Medical Faculty Associates is an equal opportunity/affirmative action employer.
W-IN2N.409.1X

Florida

Immediate Opening for internist or internist/intensivist for multidiscipline inpatient practice in Northeast Florida. Please fax your CV to: 904-398-6230.
W-IN2N.361.4X

Idaho

Southern Idaho: Intermountain Health Care (IHC) is seeking one BC-BE internist for private practice in Burley. Office space is located in the medical office building next to Cassia Regional Medical Center, a 40-bed IHC facility that opened in 1995. Two-year salary guarantee. Share office and expenses with two other internists if desired. Relocation provided. Send/fax CV to: IHC Physician Services, Attn: Wilf Rudert, 36 South State Street, 20th Floor, Salt Lake City, UT 84111. 800-888-3134 #1. Fax: 801-442-2999. E-mail: comdixon@ihc.com. Web: www.ihc.com/xp/ihc/physician/recruiting.
W-IN2N.273.3X

Illinois

Illinois, Primary Care. Excellent opportunity for BC-BE primary care physician to join the Rockford Outpatient Clinic, a satellite clinic of the Wm. S. Middleton Memorial Veterans Hospital, Madison, WI. The clinic operates M-F, 8-4:30. Position offers competitive salary and excellent benefits. Send CV to Mary Maestrelli, Human Resources, VA Hospital, 2500 Overlook Terrace, Madison, WI 53705. Phone 608-280-7026; e-mail: mary.maestrelli@med.va.gov. AA/EOE. Women and minorities encouraged to apply. US citizenship or permanent resident status required.
W-IN2N.412.1X

www.acponline.org/careers

Indiana

Northwest Indiana. Seeking BC-BE internist for primary care opportunity. Premier group in the community. Shared call. Great earning potential. Easy access to Chicago and Lake Michigan. Contact Rico Williams at 800-851-8805, x3730; fax 314-726-0026; e-mail rwilliams@cejka.com. ID#21296IA. For more opportunities, visit www.cejka.com.
W-IN2N.421.1X

Louisiana

BC-BE Internist W/WO Subspecialty for full-time LSUHSC faculty position that balances teaching in-patient medicine to FP residents, medical students, PA students, and providing hands-on care to indigent patients. Clinical research opportunities. Relative freedom from business and administrative concerns. Malpractice coverage provided. Not a J1 Visa site. LSUHSC is an Affirmative Action/Equal Opportunity employer. Contact Rick Cavell MD, FACP, 318-330-7607, PO Box 1881, Monore, LA 71202; rcavel@lsuhsc.edu.
W-IN2N.408.3X

Massachusetts

Harvard Vanguard Medical Associates has excellent full-time opportunities for BC-BE Internal Medicine physicians. Located in Boston and surrounding suburbs, with 15 locations, we are expanding our Internal Medicine Departments in our practices that are affiliated with Brigham and Women's Hospital. Our well-established, multispecialty group practice combines a supportive staff, automated medical record system and some of the brightest, most dedicated practitioners in medicine. We offer competitive salaries, flexible call schedule, a generous benefits package and teaching and research opportunities through our affiliation with Harvard Medical School. Please forward CV to Laura Schofield, Physician Recruitment, Harvard Vanguard Medical Associates, 275 Grove Street, Suite 3-300, Newton, MA 02466-2275. Fax 617-559-8255; E-mail: laura_schofield@vmed.org; or call: 800-222-4606, or 617-559-8275 within MA. EOE/AA.
W-IN2N.391.2X

Montana

Montana. You've Earned it. Things are different here. We have the technology and personnel to help your practice grow and patients who need and appreciate your skills. The Great Falls clinic is seeking a BC-BE internist for a rapidly expanding 100+ provider, multispecialty organization. We offer a benefit package and salary leading to partnership. If interested, send CV and professional goals to: Jeff Hinz, MD, Medical Director, PO Box 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com. Web site: www:gfclinic.com.
W-IN2N.420.1X

advertise here

Internal Medicine and Primary Care *continued*

New Hampshire

Exceptional Opportunity for Board Certified Internist. Subspecialty training required. Excellent compensation; benefit package. 1:6 call. Live in charming New England community near major ski area. 2-1/2 hours from Boston No J-1/H-1B opportunity. Contact Susan Edson: New England Health Search, 63 Forest Avenue, Orono ME 04473. Telephone 207-866-5680, Fax 207-866-5696, sedson@nehealthsearch.com.
W-IN2N.314.6X

New Jersey

Internal Medicine. New Jersey: Board certified internist with or without subspecialty for busy multiphysician office. Must have immigration visa or US citizen. Send resume to: Syed S. Ahmad, MD PA, 183 Franklin Corner Road, Lawrenceville, New Jersey 08648.
W-IN2N.422.1X

Office Space Available with an established Internist for full-time or part-time opportunity to build a practice. Premier untapped located (North Brunswick, New Jersey). Call for details, Robert J. Casper, MD 732-297-8666.
W-IN2N.431.1X

North Carolina

Internal Medicine Practice opportunities available in North Carolina's fastest growing area. Excellent opportunities and quality of life in Union County, south of Charlotte. For more information contact Dan Shive, Physician Services, Union Regional Medical Center, Monroe, NC. 704-283-3468, dan.shive@carolinashealthcare.org.
W-IN2N.416.2X

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for details

North Dakota

Ideal Sportsman Internal Medicine Opportunity in the Midwest. Dakota Clinic, Ltd, in Jamestown, North Dakota, is seeking a BC-BE internal medicine physician to assume a busy existing practice. Responsibilities will include inpatient in a recently remodeled 57-bed hospital and outpatient in a nearby updated clinic. The call responsibilities will be one in five. Dakota Clinic offers a competitive salary with full benefits and a two year stockholder track. Jamestown is a growing community with a diverse economy of 16,000 nestled in the picturesque James River Valley located ninety miles west of Fargo, North Dakota. A full spectrum of hunting and fishing activities are at your doorstep. Two shopping malls, excellent schools, a four year liberal college, full service YMCA with indoor olympic pool, public outdoor pool and adjacent large lake provide families with ample choices of fun activities. To learn more about this opportunity forward your CV to: Dick Reis, Physician Recruitment Manager, Dakota Clinic, Ltd., 1702 South University Drive, Fargo, ND 58103; Fax 701-364-3229 Toll free 800-882-7310; E-mail: dreis@dakcl.com. Website www.dakotaclinic.com.
W-IN2N.337.6X

Oregon

Internist BC-BE. Group practice in the glorious Blue Mountains of Eastern Oregon. Abundant outdoor recreation, scenic beauty. Strong regional rural hospital with MRI/CT, ER, and surgical specialists. Call only 1:9. Ambulatory care and inpatient skills needed. Competitive salary guarantee. No J-1 openings. Fax CV to Richard Minogue, MD 541-962-7398.
IN2N.350.6X

General Internist, Great opportunity with stable, growing, physician owned multispecialty group in Willamette Valley, Oregon. First year salary guaranteed. Cannot support J-1 visa. Contact Administrator, 503-391-1110, Fax 503-370-4237, email: Copleyp.@drsclinic.com.
W-IN1N.710.1X

Pennsylvania

Pennsylvania Seeking BC-BE internist with training, experience or interest in geriatric care. Salaried position with established geriatrician involves inpatient and outpatient care, resident teaching and shared call 1 in 3. Practice is located in the Lehigh Valley, just 60 miles north of Philadelphia and 60 miles west of NYC. Offering competitive salary and excellent benefits package including paid medical malpractice. Contact Physician Recruiting Department at Lehigh Valley Hospital. Phone 610-402-7008, fax 610-402-7014 or email Pamela.Adams@lvh.com.
W-IN2N.423.2X

Philadelphia Suburb: Seeking Internal Medicine BC-BE to join established growing practice. Comprehensive salary and benefit package. Fax CV with cover letter to Fax # 215-579-0806.
W-IN2N.410.3X

Are You Interested in Working on the bleeding edge of business and healthcare? Do you want to have fun again? Join a Philadelphia based, physician-owned and operated organization that is helping hospitals and doctors regain control of healthcare. Full-time positions available. Please fax CV to 610-446-6860 or e-mail to info@ehrdocs.com.
W-IN2N.377.3X

Texas

Houston Area-Internal Medicine. Income potential in the top 10%. Call schedule 1:7. Partnership after 1 year. Located in Conroe, TX, just 30 minutes from Bush Intercontinental and 15 minutes from The Woodlands. Enjoy fast access to Houston, Lake Conroe, and 2 national forests. Contact Erin Row (x3317) or Diane Safner (x3706) at 800-851-8805; fax 314-726-0026; e-mail dsafner@cejka.com. ID#21450IA. For more opportunities, visit www.cejka.com.
W-IN2N.424

Virginia

Opportunity is Knocking! Fredericksburg, Virginia. Seldom has an opportunity come along like this to create/establish a new internal medicine private practice group of 2-4 BE-BC internists in Fredericksburg, Virginia. This growing community, located just one hour south of Washington DC in beautiful Virginia, is the ideal place to live and practice. It offers wonderful quality of life and an growing patient base. This is the opportunity of a lifetime. The Mary Washington Hospital is a 318-bed state-of-the-art facility with a medical staff of 330 physicians and is building a 94-bed addition to be completed in January 2004. Combine this with great earning potential and you can see why opportunity is knocking for you in Fredericksburg. Come and practice medicine where you are the difference. Contact Select, inc. by calling 877-499-9889 or fax your CV to 877-855-0618 or email us at tim@selectprofessional.com for more of the exciting details of this opportunity today!
W-IN2N.427.2X

Alexandria Virginia: Eight internists internal medicine group seeks physician to join us in the practice of general internal medicine. Located in Alexandria Virginia adjacent to Mount Vernon Hospital ten miles from Washington, D.C. Busy hospital and out patient practice. Send CV to: Mount Vernon Internal Medicine 8109 Hinson Farm Road Suite 504 Alexandria, Virginia 22306.
W-IN2N.306.1X

Washington

Washington State, Puget Sound Area: 2 BC internists seeking BC-BE to assume retiring MD's established practice. Excellent opportunity and benefits in pleasant surroundings with convenient access to the Seattle Metropolitan area. No J-1 opportunities. Send cover letter and CV to: Olympic Internal Medicine Associates, 2641 Cherry Avenue, Bremerton, WA 98310. Attn: Jennifer or fax CV with cover letter to 360-373-4988.
W-IN2N.398.6X

Internal Medicine and Primary Care *continued*

Wisconsin

Wisconsin- The Wisconsin Office of Rural Health currently has detailed information on over 25 general internal medicine positions located in both rural communities and larger cities in almost every area of the state. WORH is a non-profit program that has been helping family physicians find rewarding and satisfying positions in Wisconsin for over 23 years and is located at the University of Wisconsin Medical School. For a complete listing of all positions available, please contact: Randy Munson, Wisconsin Office of Rural Health, 109 Bradley Memorial, 1300 University Avenue, Madison, WI 53706. 800-385-0005 (rlmunson@wisc.edu).
W-IN2N.436.12X

Wisconsin, Primary Care. Excellent opportunity for BC-BE primary care physician to join the Wm. S. Middleton Memorial Veterans Hospital, Madison, WI. The hospital is a 90-bed med-surg facility affiliated with the University of WI. Responsibilities include primary care, some inpatient attending, and teaching students and residents. Competitive salary and excellent benefits. Madison is a prestigious college town offering personal and professional development. Send CV to Mary Maestrelli, Human Resources, VA Hospital, 2500 Overlook Terrace, Madison, WI 53705. Phone 608-280-7026; e-mail: mary.maestrelli@med.va.gov. AA/EOE. Women and minorities encouraged to apply. US citizenship or permanent resident status required.
W-IN2N.413.1X

Cardiology

Pennsylvania

Wanted BE-BC Cardiologist and internist/FP. J-1 approved site. Respond to Box AIM-152N. Annals of Internal Medicine, 190 North Independence Mall West, Philadelphia, PA 19106-1572.
W-CA2N.415.1X

Send box Replies To:

Reply Box AIM-XXX
Annals of Internal Medicine
190 N. Independence Mall W.
Sixth Street at Race
Philadelphia, PA 19106

Emergency Medicine

California

Doctors Hospital of Manteca has immediate openings for BP/BC EM or Primary Care Specialty physicians with ED experience. Newly remodeled emergency department sees 16,000 annual visits and has an experienced staff of excellent physicians and acillary staff. Manteca is conveniently located in the beautiful San Joaquin Valley of California, within a short distance to San Francisco, Sacramento, Yosemite and Lake Tahoe. Manteca offers unique shops, a family atmosphere, and an abundance of recreational activities, making it an ideal location. We offer competitive compensation, paid professional liability insurance coverage, pre-tax spending account and retirement plan, and $2,000 CME per year. Contact Dani Taylor, CPC, at 800-362-2731, dani_taylor@emcare.com. or fax CV to 214-712-2444. EOE.
W-EM2N.430.1X

New York

New York, Mountain Lake Region: Medical Director needed at regional hospital (www.cvph.org) with annual census of 42,600. New emergency care center, adjacent fast track. Hospital employed position with 12 other physicians and excellent compensation package. Plattsburgh offers a wonderful family environment with a wide variety of social, cultural, and recreational opportunities available in Montreal and Lake Placid-Olympic region. Contact Lisa VanNatten, CVPH Medical Center, 75 Beekman St., Plattsburgh, NY 12901, 800-562-7441, fax 518-562-7012, Lvannatten@cvph.org.
W-EM2N.375.2X

Endocrinology

Minnesota

Central Minnesota: Great opportunity for one or two BC-BE Endocrinologists to join three Endocrinologists in a progressive 134-physician multispecialty clinic with an excellent referral base. Our diabetes program, which recently moved into a new building, was recently recognized by the ADA as a comprehensive diabetes center with certified diabetes educators and dieticians. The clinic practice involves general endocrinology and diabetes with a 1:4-5 call schedule. This growing Central Minnesota community serving a referral area of 575,000 offers an outstanding lifestyle with three colleges, excellent public and private schools and abundant recreational activities. St. Cloud is located on the Mississippi River and is one hour from the Twin Cities on premier lakes area. Attractive compensation and benefits package. Opportunity available for teaching in Family Practice Residency and in surrounding medical communities. Please contact: Karla Donlin, Physician Recruiter, St. Cloud Hospital, 1406 Sixth Avenue North, St. Cloud, MN 56303. 800-835-6652. E-mail: donlink@centracare.com.
W-EN1N.727.TF

Gastroenterology

District of Columbia

Gastroenterologist needed for established consultative group practice in suburban Washington, DC with shared independent ASC. BC-BE, personable, sincere, motivated team player, and well trained for full/part-time position. Competitive salary/benefits leading to partnership. Practice experience a plus. Send CV and cover letter. Reply Box AIM-150N. C/O ACP-ASIM, 190 N. Independence Mall West, Philadelphia, PA 19106.
W-GA2N.379.3X

Minnesota

St.Cloud, Minnesota: the CentraCare Center is recruiting a BE-BC gastroenterologist to join a well-established group of eight gastroenterologists at the newly constructed CentraCare Health Plaza. Therapeutic endoscopic skills and ERCP/ERS training required. EUS training desirable. CentraCare Clinic, a 134-physician, multispecialty clinic with 10 clinic locations, offers a competitive compensation and benefits package. St. Cloud, located on the banks of the Mississippi River is 60 miles northwest of Minneapolis/St. Paul and the Brainerd/Alexandria lakes area. Three colleges and numerous private and public primary and secondary schools provide excellent educational options for children and adults. Call or send CV to: Kristine Cunningham Rose Physician Recruiter St. Cloud Hospital, 1406 Sixth Avenue North St. Cloud, MN 56303. 800-835-6652 ext. 54188 fax 320-255-5711 e-mail: cunninghamrosek@centracare.com www.centracare.com.
W-GA1N.547.TF

Hematology/Oncology

Colorado

Denver, Colorado Colorado Permanente Medical Group Clinical Position. BC-BE hematologist/oncologist to join growing 576 physicians multispecialty HMO in the Denver metropolitan area. CPMG, a prepaid group practice caring for members of the Kaiser Foundation Health Plan, is seeking an additional hematologist/oncologist. Salaried position not affected by Chemotherapy reimbursement issues. Clinical trials participation, oncology pharmD, teach house staff. Excellent salary and benefit package including paid professional liability insurance. Contact: Physician Recruitment, CPMG, 10350 E. Dakota Ave., Denver, CO. 80231. Phone: 303-344-7838, Fax: 303-344-7818. EOE, M/F, V/H.
W-HE2N.256.1X

www.acponline.org/careers

Hospitalists

California

San Jose and CA Coast Hospitalist Opportunities. Equity partnership opportunities in a new Hospitalist program. Be part of building and molding young dynamic practice. Significant growth potential. Minimum start-up salary of $160,000 plus bonus. Visit our website: www.medamerica.com. Contact Ann Wareham, MedAmerica, 2101 Webster Street, Suite 1700, Oakland, CA 94612. Phone 800-842-2619; fax 510-663-0113; e-mail: recruiting@medamerica.com.
W-HP2N.396.3X

Florida

Immediate Opening for internist or internist/intensivist for multidiscipline inpatient practice in Northeast Florida. Please fax your CV to: 904-398-6230.
W-HP2N.362.

Maine

Top-Rated Small City. Unique, exciting opportunity for BC-BE internist. Work closely with strategically well-positioned practices in sophisticated medical community. Shift-work schedule. Competitive salary, benefits, student loan assistance. Family environment near lakes, mountains, ocean, state university. No J-1/H1-B opportunity. Contact Susan Edson: New England Health Search, 63 Forest Avenue, Orono, ME 04473. Phone 207-866-5680, Fax 207-866-5696, sedson@nehealthsearch.com.
W-HP2N.349.3X

Excellent opportunity for BC-BE Internist. 200-bed community hospital. Salary plus incentive; student loan assistance. Live in community with top-rated schools. Close to Portland, seacoast, mountains. (No J-1/H1-B site.) Contact Susan Edson, New England Health Search, 63 Forest Avenue, Orono, ME 04473. Telephone 207-866-5680, Fax 207-866-5696, sedson@nehealthsearch.com.
W-HP2N.244.3X

Massachusetts

Internal Medicine-Hospitalist Boston, MA, New England Baptist Hospital 1.) Full time weekends 7a-7p (weekend incentive pay) 2.) Part time- nights (multiple night positions available) Must have current ACLS, Massachusetts license, U.S., DEA, Massachusetts Physician registration, BC-BE in Internal Medicine, and eligible for credentials in Medicare, Medicaid and private insurances. Please e-mail: CV to aholt@caregroup.harvard.edu.
W-HP2N.438.4X

Classified ads on
World Wide Web:
www.acponline.org/careers

Mississippi

Hospitalist Opportunity in Beautiful Brookhaven, Mississippi. This county of 30,000 is located just 45 minutes south of Jackson and one hour north of New Orleans. They are looking for two physicians to work at their 122-bed hospital. Account is offering a base salary of $130,000 plus excellent benefits and moving expenses. Call Robert Evan, MDA, 800-866-7987; Fax 800-428-2520; or e-mail: evansr@mdainc.com.
W-HP2N.399.4X

Montana

Montana. You've Earned it. Things are different here. We have the technology and personnel to help your practice prosper and patients who need and appreciate your skills and energies. The Great Falls Clinic, LLP is seeking a BC-BE hospitalist to join our 100+ providers. No outpatient responsibilities. Strong support from 26-member internal medicine department. Hospital resources available. We offer a benefit package and salary leading to partnership. If interested, send CV and professional goals to: Jeff Hinz, MD, Medical Director, PO Box 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com. Web site: www.gfclinc.com.
W-HP2N.419.1X

South Carolina

South Carolina- Southeastern Emergency Physicians, a Team Health affiliate, has several hospitalist opportunities for Hospitalist programs in Aiken and Greenville. Physicians must be BC or BE in Internal Medicine and residency trained with experience preferred. Aiken is in thoroughbred country; has a rich history and is known for its beautiful golf course. Greenville is located between Atlanta and Charlotte, and is only 15 minutes away from the Blue Ridge Mountains. Team Health offers competitive compensation, paid professional liability insurance and a flexible schedule. For more information, call Kaye Osborne at 800-539-0173, ext. 5618; fax your CV to 865-670-2806; or e-mail: kaye_osborne@teamhealth.com.
W-HP2N.437.1X

West Virginia

Hospitalist Physician-Board Certified in internal medicine for Martinsburg VA Medical Center (located within 1 hour of Baltimore and Washington DC)). Fax CV including citizenship status to Penny Blake at 304-262-7433.
W-HP2N.407.1X

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Infectious Disease

Florida

Infectious Disease and Travel Medicine. Popular South Florida location! Booming practice with interesting and varied pathology. ID and travel medicine. Competitive salary based on experience plus comprehensive benefits. In and outpatient practice. Interviews and information, call Marci at 888-637-3272 (888MEDSEARCH, Inc.) or e-mail Marci@1888mdsearch.com, fax 954-236-3669. Visit our website: www.1888mdsearch.com.
W-ID2N.417.1X

Ohio

BC ID-IM consultant seeks BC-BE, ID-IM associate in Ohio. Respond to Box AIM-153N.
W-ID2N.414.4X

Utah

The Division of Infectious Diseases at the University of Utah seeks applications for an Assistant/Associate Professor or Professor for a full-time position in the tenure, clinical or research track in the HIV care program at the University of Utah School of Medicine. Applicants should be BC-BE in Infectious Disease and have significant HIV experience. Responsibilities include outpatient care, inpatient consultations, supervision of clinical research as well as housestaff and medical student teaching. Direct inquiries with CV and three letters of reference to: Kristen Ries, MD, Department of Medicine, Division of Infectious Diseases, 30 N. 1900 East, 4B319, Salt Lake City, UT 84132. The University of Utah is an EEO/AA employer and encourages applications from women and minorities.
W-ID2N.425.2X

Assistant Professor of Medicine. Two full-time faculty positions in the Division of Infectious Diseases, University of Utah School of Medicine. Applicants must be BC in Infectious Diseases with a strong interest in teaching and patient care. The first position requires interest and experience in geographical/travel medicine, management of orthopedic infections and medical informatics. The second position requires experience in supervision of a clinical microbiology laboratory in a tertiary referral hospital and in investigation of immunology of human falciporum malaria. Please send letter of interest and CV to John Hibbs, MD, Chief of Infectious Diseases, University of Utah School of Medicine, 30 N. 1900 East, 4B319, Salt Lake City, UT 84132. The University of Utah is an EEO/AA employer and encourages applications from women and minorities.
W-ID2N.433.2X

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Virginia

Veterans Affairs Medical Center in Salem, Virginia is currently a Board-Certified/Board Eligible general internist for primary care. Responsibilities include primary care clinical practice and teaching in a team setting. Seeking physician with interest in leadership and program development. Department of Veterans Affairs offers a generous retirement plan, vacation/holiday pay, sick leave, and health/life insurance. Salary commensurate with experience. Practice is enhanced by location in the beautiful Blue Ridge Mountains of Southwest Virginia. The area has excellent schools as well as two 4-year colleges in the valley. Fax CV and references to Marshall Daniels, Human Resources Management Specialist at 540-224-1929. EOE.
W-ID2N.426.1X

Nephrology

Florida

Nephrologist needed to join established nephrology practice in Florida Gulf Coast. Competitive salary/benefits leading to early partnership. CV to Box AIM-154N.
NP2N.432.6X

Pulmonary Medicine

Montana

Montana...You've Earned it. We have the technology and personnel to help your practice prosper who need and appreciate your skills and energies. Great Falls Clinic, LLP is seeking a BC-BE pulmonary or critical care specialist. We offer a benefit package and salary leading to partnership. Does not qualify for J-1 waiver status. Please send CV and professional goals to: Jeff Hinz, Medical Director, PO Box 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com. Web site: www.gfclinic.com.
W-PU2N.418.1X

West Virginia

Intensivist Full-Time Board certified in pulmonary/critical care for Martinsburgh VA Medical Center (Located within 1 hour of Baltimore and Washington DC). Opportunity for teaching clinical research. Fax including citizenship status to Penny Blake at 304-262-7433. EOE.
W-PU2N.406.1X

Linking Physicians with Positions.

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Rheumatology

Colorado

Denver, Colorado Kaiser Permanente Rheumatology: Colorado Permanente Medical Group, P.C., a large multispecialty group serving Kaiser Permanente members, is seeking a BE/BC rheumatologist for an innovative pure subspecialty practice. Major teaching hospital affiliated. Competitive salary and an excellent benefit package. Denver has abundant four-season outdoor activities enhanced by many community amenities. If interested please contact Physician Recruitment, at Colorado Permanente Medical Group, 10350 E. Dakota Avenue, Denver, Colorado 80231-1314, 303-344-7838 or fax your CV with a cover letter to Physician Recruitment at 303-344-7818.
W-RH2N.792.5X

Massachusetts

Massachusetts, Cambridge. Harvard teaching hospital seeks BC/BE rheumatologist to take over in high-demand environment. Please fax CV to 617-499-5620.
W-RH2N.343.4X

Miscellaneous

National

Pharmaceutical Career Opportunities. We have assignments for entry and experienced physicians in the pharmaceutical industry. Send your curriculum vitae in confidence to Bruce Rogers Company, Management Consultants, 20 Main Street, Port Washington, NY 11050; 516-883-1058. E-mail: BRUROGCO@aol.com.
W-MS4N.545.6X

Residencies and Fellowships

New Jersey

Unexpected Two Openings - Clinical non-invasive Cardiology PGY IV position is available beginning July 1, 2002. This is a one-year program and is not accredited by the ACGME. The candidate must be a Board-eligible or Board-certified internist. Interested applicants, please fax your CV to the Cardiology Office Manager, Jackie Mayes at 201-915-2443.
W-RF2N.397.3X

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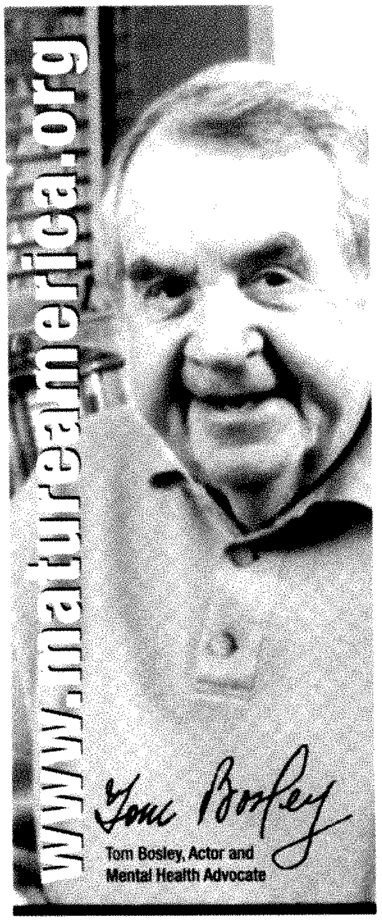

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A GUIDE FOR THE PRIMARY CARE PHYSICIAN

Edited by Janice Ryden, MD, FACP,
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The latest book in the ACP Women's Health Series covers a broad range of gynecologic problems commonly managed in an office setting. Fundamentals are reviewed, and detailed evidence-based information on a wide variety of subjects is presented. Practical guidance is provided on topics such as examination and screening, menstrual disorders, sexually transmitted diseases, contraception, breast problems, and menopause.

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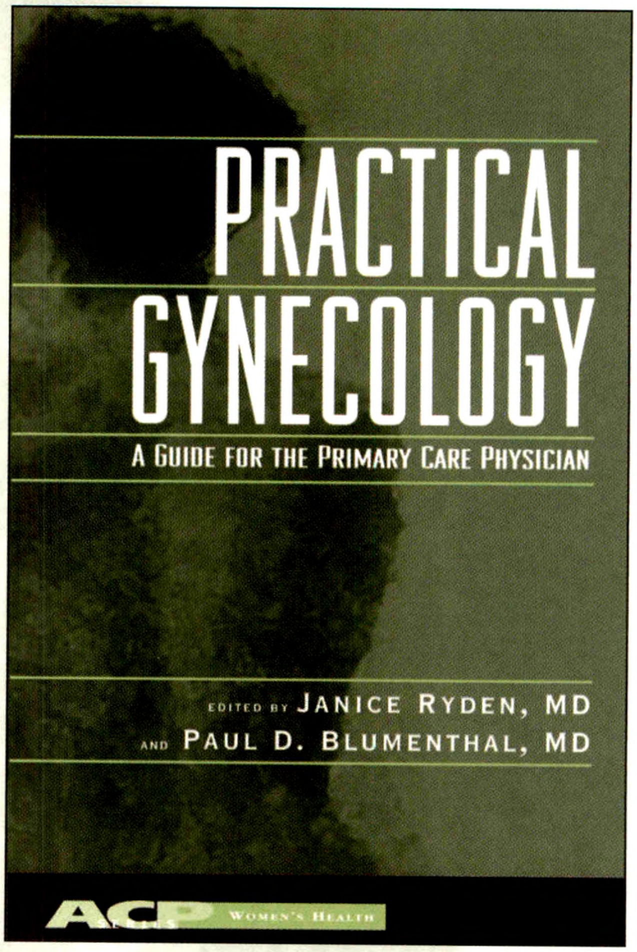

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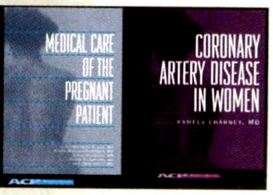

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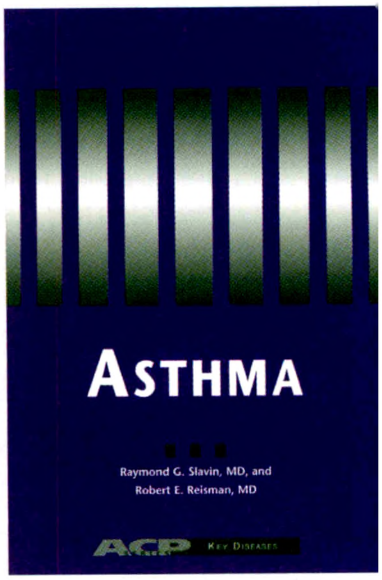

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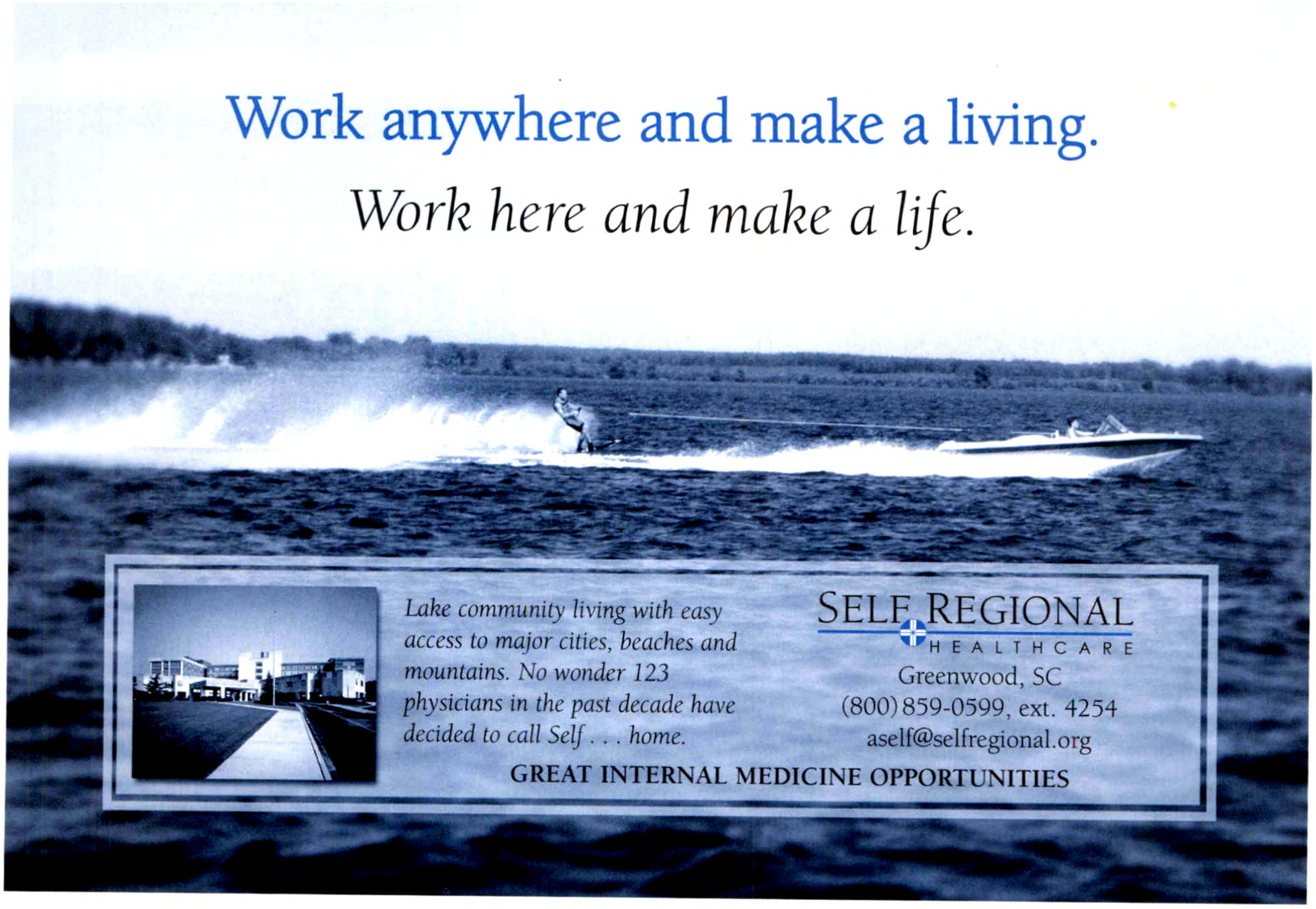

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Director, Recruitment Services
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Internist

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Call: (800) 488-2240
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Lila M. Lokey
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VA Great Lakes Health Care System

eoe

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>
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>
> Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.
>
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- Lovenox Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:
  - in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
  - in patients undergoing hip replacement surgery, during and following hospitalization;
  - in patients undergoing knee replacement surgery;
  - in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.
- Lovenox Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.
- Lovenox Injection is indicated for:
  - the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism,** when administered in conjunction with warfarin sodium;
  - the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

See **DOSAGE AND ADMINISTRATION: Adult Dosage** for appropriate dosage regimens.

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection.

WARNINGS

Lovenox Injection is not intended for intramuscular administration.

Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox Injection.

Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism **(see PRECAUTIONS: Pregnancy).**

PRECAUTIONS

General: Lovenox Injection should not be mixed with other injections or infusions.

Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Lovenox Injection should be used with care in these patients. Adjustment of enoxaparin sodium dose may be considered for low weight (<45 kg) patients and/or for patients with severe renal impairment (creatinine clearance <30 mL/min).

If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).

Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves).**

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women.

Pediatric Use: Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.

Geriatric Use: Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered. (see **CLINICAL PHARMACOLOGY** and **General** and **Laboratory Tests** subsections of **PRECAUTIONS**)

ADVERSE REACTIONS

Hemorrhage: The incidence of major hemorrhagic complications during Lovenox Injection treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection.

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

	Dosing Regimen	
Indications	**Lovenox Inj.** 40 mg q.d. SC	**Heparin** 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery[1]

	Dosing Regimen		
Indications	**Lovenox Inj.** 40 mg q.d. SC	**Lovenox Inj.** 30 mg q12h SC	**Heparin** 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis[2]		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period[3]	n = 288 4 (2%)		
Extended Prophylaxis Period[4]	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis[2]		n = 294 3 (1%)	n = 225 3 (1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

[2] Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

[3] Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

[4] Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

	Dosing Regimen		
Indications	**Lovenox Inj.[2]** 20 mg q.d. SC	**Lovenox Inj.[2]** 40 mg q.d. SC	**Placebo[2]**
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

	Dosing Regimen	
Indication	**Lovenox Inj.[1]** 1 mg/kg q12h SC	**Heparin[1]** aPTT Adjusted i.v. Therapy
Unstable Angina and Non-Q-Wave MI[2,3]	n = 1578 17 (1%)	n = 1529 18 (1%)

[1] The rates represent major bleeding on study medication up to 12 hours after dose.

[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).

[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment[1]

	Dosing Regimen[2]		
Indication	**Lovenox Inj.** 1.5 mg/kg q.d. SC	**Lovenox Inj.** 1 mg/kg q12h SC	**Heparin** aPTT Adjusted i.v. Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

[2] All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox Injection or standard heparin therapy and continuing for up to 90 days

Thrombocytopenia: see **WARNINGS: Thrombocytopenia**.

Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox Injection should be interpreted with caution.

Local Reactions: Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox Injection.

Other: Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Abdominal or Colorectal Surgery

	Dosing Regimen			
	Lovenox Inj. 40 mg q.d. SC n = 1228		**Heparin** 5000 U q8h SC n = 1234	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Ecchymosis	0%	3%	0%	3%

[1] Excluding unrelated adverse events.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Hip or Knee Replacement Surgery

	Dosing Regimen									
	Lovenox Inj. 40 mg q.d. SC				**Lovenox Inj.** 30 mg q12h SC		**Heparin** 15,000 U/24h SC		**Placebo** q12h SC	
	Peri-operative Period n = 288 [2]		Extended Prophylaxis Period n = 131 [3]		n = 1080		n = 766		n = 115	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	0%	8%	0%	0%	<1%	5%	<1%	4%	0%	3%
Hemorrhage	<1%	13%	0%	5%	<1%	4%	1%	4%	0%	3%
Nausea					<1%	3%	<1%	2%	0%	2%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%	<1%	7%
Edema					<1%	2%	<1%	2%	0%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%	<1%	4%	0%	3%

[1] Excluding unrelated adverse events.

[2] Data represents Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.

[3] Data represents Lovenox Injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Medical Patients[1] With Severely Restricted Mobility During Acute Illness

	Dosing Regimen	
Adverse Event	**Lovenox Inj.** 40 mg q.d. SC n = 360 %	**Placebo** q.d. SC n = 362 %
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

[1] Excluding unrelated and unlikely adverse events.

Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction: Non-hemorrhagic clinical events reported to be related to Lovenox Injection therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox Injection than in patients treated with i.v. heparin. Serious adverse events with Lovenox Injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox Injection group, are provided below (irrespective of relationship to drug therapy).

Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

	Dosing Regimen	
Adverse Event	**Lovenox Inj.** 1 mg/kg q12h SC n = 1578 n (%)	**Heparin** aPTT Adjusted i.v. Therapy n = 1529 n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen					
	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		**Lovenox Inj.** 1 mg/kg q12h SC n = 559		**Heparin** aPTT Adjusted i.v. Therapy n = 544	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0%	5%	0%	3%	<1%	<1%
Injection Site Pain	0%	2%	0%	2%	0%	0%
Hematuria	0%	2%	0%	<1%	<1%	2%

[1] Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Other Ongoing Safety Surveillance Reports: local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see **WARNINGS, Thrombocytopenia**). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE

Symptoms/Treatment: Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection. A second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.

A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSAGE AND ADMINISTRATION

All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see **PRECAUTIONS, Laboratory Tests**).

Note: Lovenox Injection is available in two concentrations:

1 100 mg/mL Concentration: 30 mg / 0.3 mL ampules, 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes.
2 150 mg/mL Concentration: 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:

Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.

Medical Patients During Acute Illness. In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.

Administration: Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

When using Lovenox Injection ampules, to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended.

Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device.

Keep out of the reach of children.

Rx Only.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.

Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807
Prescribing information as of July 2001.
lovb0701Aa

Just when you thought heparin should be working[1]...
Was it?
LOVENOX establishes predictable antithrombotic activity from dose one.*
LOVENOX®
(enoxaparin sodium) Injection
TM
THERAPEUTIC FROM DOSE ONE

IMPORTANT SAFETY INFORMATION

LOVENOX (enoxaparin sodium) Injection cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular-weight heparins or heparinoids are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of postoperative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis. Patients should be frequently monitored for signs and symptoms of neurological impairment. (See boxed WARNING.)

As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX therapy. Bleeding can occur at any site during LOVENOX therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. (See WARNINGS.)

Thrombocytopenia can occur with LOVENOX. In patients with a history of heparin-induced thrombocytopenia, LOVENOX should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000 mm^3, LOVENOX should be discontinued. Cases of heparin-induced thrombocytopenia have been observed in clinical practice. (See WARNINGS.)

The use of LOVENOX is not recommended for thromboprophylaxis in patients with prosthetic heart valves. (See WARNINGS.)

LOVENOX is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding.

For more information, contact your local Aventis Pharmaceuticals Representative or call Aventis Pharmaceuticals Medical Information at 1-800-633-1610.

Reference: 1. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-452.

Please see brief summary of prescribing information, including boxed WARNING, on adjacent pages.
Visit our website, www.LOVENOX.com, for professional and patient information.

*No routine coagulation monitoring required.

Aventis Pharmaceuticals

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The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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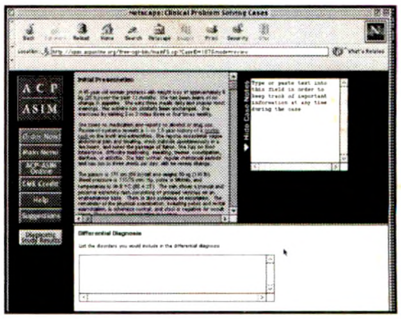

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K.S. Kinchen, J. Sadler, N. Fink, R. Brookmeyer, M.J. Klag, A.S. Levey, and N.R. Powe

Late evaluation of patients with chronic renal failure by a nephrologist is associated with greater burden and severity of comorbid disease, black ethnicity, lack of health insurance, and shorter duration of survival.

Sex Differences in Cardiac Catheterization after Acute Myocardial Infarction: The Role of Procedure Appropriateness 487

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T.D. Rea, S.R. Heckbert, R.C. Kaplan, N.L. Smith, R.N. Lemaitre, and B.M. Psaty

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In 1914, Lewellys F. Barker, William Osler's successor as Professor of Medicine at the Johns Hopkins University School of Medicine and physician-in-chief at the Johns Hopkins Hospital, resigned to enter private practice rather than accept the terms of a full-time plan, whereby professors in clinical departments would receive fixed salaries and have no financial incentives to see patients. The predicaments he faced in 1914 continue to pester the medical profession in the United States.

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Screening for Postmenopausal Osteoporosis: A Review of the Evidence for the U.S. Preventive Services Task Force 529

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Annals of Internal Medicine | ARTICLE

The Timing of Specialist Evaluation in Chronic Kidney Disease and Mortality

Kraig S. Kinchen, MD, MSc; John Sadler, MD; Nancy Fink, MPH; Ronald Brookmeyer, PhD; Michael J. Klag, MD, MPH; Andrew S. Levey, MD; and Neil R. Powe, MD, MPH, MBA

Background: **Care for chronic renal failure involves management of complications and preparation for possible dialysis. Patients often are not evaluated by nephrologists in a timely manner.**

Objective: **To identify factors associated with late evaluation by a nephrologist and to assess whether late evaluation is associated with worse survival once patients develop end-stage renal disease (ESRD).**

Design: **National prospective cohort study.**

Setting: **81 dialysis facilities throughout the United States.**

Patients: **828 patients with new-onset ESRD.**

Measurements: **Time from first evaluation by a nephrologist to initiation of dialysis, classified as late (<4 months), intermediate (4 to 12 months), or early (>12 months); rate of death, from initiation of dialysis to an average of 2.2 years of follow-up; and demographic, clinical, and laboratory characteristics.**

Results: **After adjustment for potential confounders, late evaluation was more common among black men than white men (44.8% vs. 24.5%; $P < 0.05$), uninsured patients than insured patients (56.7% vs. 29.0%; $P < 0.05$) and patients with severe comorbid disease than those with mild comorbid disease (35.0% vs. 23.0%; $P < 0.05$). Compared with patients who had early evaluation, the risk for death was greater among patients evaluated late and was graded (hazard ratio, 1.3 [95% CI, 0.87 to 2.06] for patients with intermediate evaluation and 1.8 [CI, 1.21 to 2.61] for those with late evaluation) after adjustment for dialysis method, demographic characteristics, and socioeconomic status in Cox proportional hazards regression analysis. After additional adjustment for such factors as the presence and severity of comorbid conditions, the association remained graded (hazard ratio, 1.2 [CI, 0.73 to 1.82] for patients evaluated at an intermediate point and 1.6 [CI, 1.04 to 2.39] for those evaluated late).**

Conclusions: **Late evaluation of patients with chronic renal failure by a nephrologist is associated with greater burden and severity of comorbid disease, black ethnicity, lack of health insurance, and shorter duration of survival.**

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See editorial comment on pp 542-543.

In the United States, approximately 300 000 persons have treated end-stage renal disease (ESRD) and an estimated 800 000 persons have a serum creatinine concentration of 177 μmol/L (2.0 mg/dL) or greater (1, 2). Annual U.S. spending related to treatment of ESRD exceeds $15 billion (3). Yet, outcomes for patients with ESRD remain relatively poor, with a 5-year survival rate of about 29% for patients undergoing dialysis (4). Whether better care of patients with ESRD earlier in their disease course improves outcomes is under increased investigation (5, 6). Many patients with chronic kidney disease may benefit from beginning their care with primary care physicians. As in the management of other chronic diseases, primary care physicians must decide whether evaluation by a specialist might improve care and, if so, when in the disease course specialist evaluation is most appropriate.

Although 39% of patients undergoing hemodialysis and 52% of those undergoing peritoneal dialysis are evaluated by a nephrologist more than 1 year before dialysis, 25% and 16%, respectively, of such patients are seen less than 1 month before dialysis (7). One argument for early evaluation by a nephrologist is that management of chronic renal insufficiency and its complications, such as anemia and renal osteodystrophy, may be improved. Early evaluation might facilitate improved patient education about dialysis; provide more time to make an informed choice about the type of dialysis; and allow timely placement of permanent vascular access, which is associated with better dialysis and fewer complications compared with temporary access (8, 9).

Late evaluation is associated with a higher risk for unplanned first dialysis, more complications, higher hospital costs, and longer duration of hospitalization in the first 3 months of dialysis (10–13). Most previous studies of late evaluation were done in countries other than the United States, involved only one center, or have had relatively short follow-up (10, 11, 13–16). We sought to determine the patient factors that are associated with late evaluation by a nephrologist in the United States and the effect of late evaluation on mortality.

METHODS

Study Design and Sample

We conducted a national, concurrent, prospective cohort study as part of the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. (For a list of all investigators on the CHOICE Study, see the Appendix.) Between October 1995 and June 1998, 1041 patients undergoing incident dialysis were enrolled at 81 dialysis clinics in 19 states (79 clinics affiliated with Dialysis Clinics Incorporated and 2 clinics affiliated with Beth Israel Medical System) (17). Median time from initiation of dialysis to enrollment was 45 days, and 98% of enrollment took

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Context

In the United States, the 5-year survival of patients undergoing dialysis is 29%. Early nephrologist evaluation is associated with better outcomes, but 25% of patients first see a nephrologist within a month of beginning dialysis.

Contribution

Late nephrology evaluation (<4 months before start of dialysis) was most common among black men, uninsured patients, and patients with severe comorbid illness. The later the first evaluation by a nephrologist, the greater the risk for death.

Clinical Implications

Clinicians need a system to remind them to refer patients at an early stage of chronic renal failure, especially black men, the uninsured, or patients with severe comorbid illness.

–The Editors

places within 4 months of initial dialysis. Patients were excluded if they were younger than 18 years of age or did not speak English or Spanish.

The Johns Hopkins University School of Medicine Institutional Review Board and the review boards of each clinical center approved the CHOICE protocol. The CHOICE Study was designed to examine the choices that patients and providers make in initiation and maintenance of renal replacement therapy, particularly the choice of hemodialysis versus peritoneal dialysis.

Data Collection

At enrollment, patients completed a baseline questionnaire on medical and social history and provided the month and year in which they first visited a nephrologist. Demographic data, insurance information, the assigned cause of renal failure, baseline laboratory values, and the date of initial dialysis were obtained from the Center for Medicare & Medicaid Services medical evidence form. A trained research nurse abstracted medical records to determine the Index of Disease Severity score for 19 medical conditions. The Index of Physical Impairment score, a measure of impairment in 11 areas, was assessed by clinic staff. The Index of Physical Impairment and Index of Disease Severity were combined to form the Index of Coexistent Disease, a measure of the burden and severity of comorbid disease that is scored from 0 or 1 (mild coexistent disease) to 3 (severe coexistent disease) (18–21). Information from clinic reports and the Center for Medicare and Medicaid Services were used to determine the date of death.

The time between first evaluation by a nephrologist and the date of first dialysis is referred to as the "time of evaluation" and was categorized as late (<4 months), intermediate (4 to 12 months), or early (>1 year). The 4-month cutoff for late evaluation has been used in other studies (13, 22). The 12-month cutoff for early evaluation was chosen because some experts recommend 1 year as the minimal time necessary to prepare a patient adequately for dialysis (23). We reviewed available medical records for patients having late evaluation and a 10% sample of remaining charts. In 13 cases, time of evaluation was adjusted from late to intermediate or early evaluation.

Three hundred thirty-four patients did not answer the question on time of evaluation. On the basis of medical record review, 70 of these patients were categorized as having early evaluation and 51 as having intermediate evaluation. For 182 of the 334 patients, the medical records showed no definite evidence to indicate evaluation by a nephrologist more than 4 months before dialysis. These patients, along with 31 patients without available medical records, were categorized as having missing data. The total sample comprises 828 patients.

Statistical Analysis

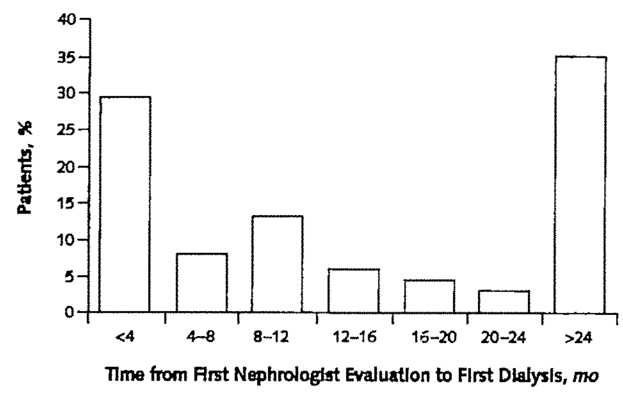
Characteristics of the sample stratified by time of evaluation were compared by using chi-square tests and analysis of variance, as appropriate. Distributions of patients according to the time of evaluation were compared by using the Wilcoxon rank-sum test for two-category comparisons and the Kruskal–Wallis test for multiple comparisons.

Unadjusted percentages of patients having late evaluation were calculated for different characteristics. Multivariate logistic regression was performed to determine the presence, magnitude, and independence of the association between patient characteristics and late evaluation. We considered the potential effect of multiple centers on our analyses (24). Given the possibility of confounding by clinic, all logistic regression analyses were conditioned on clinic (25). Patient characteristics in the multivariate conditional logistic regression model that were significantly associated ($P < 0.10$) with late evaluation in univariate analysis were considered potential confounders. Adjusted percentages were calculated on the basis of the adjusted odds ratios derived from logistic regression (26) and the relevant unadjusted frequencies of reference group in each analysis. A Hosmer–Lemeshow test was used to assess model adequacy.

We used Cox proportional hazards regression to test the presence, strength, and independence of the association between time of evaluation and mortality. Survival time was calculated from the date of first dialysis. Patients were considered to be under observation from time of enrollment until death or 30 April 2000. Patients were censored if they received a transplant, changed to a non-CHOICE clinic, or declined to participate further in the study.

To account for the possibility that differing standards of care at the various clinics explained differences in survival, all proportional hazards models were stratified by clinic (27). We first included nonmodifiable risk factors in

Figure 1. **Time from first evaluation by a nephrologist to first dialysis.**



the regression models (demographic characteristics and socioeconomic status) and then added potentially modifiable risk factors (smoking, exercise, comorbid conditions and disease severity, and laboratory values) to examine whether these factors explained associations between time of evaluation and mortality. Factors included in the final Cox proportional hazards model were significantly associated with mortality ($P < 0.10$) in univariate analysis or had been shown in the literature to have a clinically important association with mortality. Sex and type of dialysis were included a priori. Some modifiable factors may appear in the causal pathway between late evaluation and mortality. Their addition to the model might explain any observed associations. Thus, hematocrit less than 0.3 and hypoalbuminemia (serum albumin level < 36 g/L) were added to the model as potentially modifiable risk factors because previous studies have shown a relationship between these factors and ESRD mortality (28, 29). The glomerular filtration rate, which was calculated according to the Modification of Diet in Renal Disease equation (30), was included to adjust for renal function.

We performed sensitivity analyses to explore the effect of assumptions about missing data on time of evaluation and the effect of alternative categorizations of evaluation time. Statistical analyses were performed by using Stata software, version 6.0 (Stata Corp., College Station, Texas).

Role of the Funding Source

The project was funded by a grant from the Agency for Healthcare Research and Quality (Dr. Powe, principal investigator), the Robert Wood Johnson Clinical Scholars Program (Dr. Kinchen), and the National Institute of Diabetes and Digestive and Kidney Diseases (Drs. Powe and Klag). No funding source had a role in the design, conduct, or reporting of the study.

Table 1. **Patient Characteristics, Stratified by Time of Evaluation by a Nephrologist**

Characteristic	All Patients (n = 828)	Early Evaluation (n = 399)	Intermediate Evaluation (n = 184)	Late Evaluation (n = 245)	P Value
Men, %	55.2	56.6	57.6	51.0	>0.2
Black ethnicity, %	27.5	21.1	33.2	33.9	0.001
Age < 65 y, %	64.9	68.2	65.2	59.2	0.067
Employed before dialysis, %	27.9	29.9	23.9	27.6	>0.2
Group health insurance, %	31.5	38.4	26.6	24.1	<0.001
Uninsured, %	5.6	5.0	3.9	8.0	0.151
Attended college, %	37.1	44.0	28.1	32.8	<0.001
Peritoneal dialysis, %	25.2	31.3	23.4	16.7	<0.001
Hypertension, %	95.3	96.0	97.3	92.7	0.056
Diabetes mellitus, %	52.4	46.9	63.7	53.1	0.001
Mean Index of Coexistent Disease score	1.9	1.8	2.0	2.1	<0.001
Urine excretion ≥ 1 cup/d, %	79.1	86.7	86.4	75.4	0.001
Glomerular filtration rate < 0.07 mL · s^{-2} · m^{-2}, %	52.1	51.7	42.5	59.4	0.021
Exercise one or more times per week, %	20.9	26.3	17.5	14.9	0.001
Hematocrit < 0.3, %	61.8	56.0	66.0	68.1	00.008
Serum albumin level < 36 g/L, %	66.2	60.5	63.3	77.9	<0.001
Serum creatinine concentration ≥ 884 μmol/L (≥10 mg/dL), %	25.1	23.8	24.9	27.3	>0.2
Received erythropoietin before dialysis, %	23.0	25.3	31.5	12.7	<0.001
Vascular access established > 45 d before hemodialysis, %	33.5	45.4	39.7	13.4	<0.001
Mean duration of smoking, y	15.7	15.4	15.7	16.3	>0.2

Table 2. **Association between Patient Characteristics and Late Evaluation by a Nephrologist**

Characteristic	Patients with Late Evaluation, %		Adjusted Odds for Late Evaluation (95% CI)
	Unadjusted Proportion (*n* = 713)	Adjusted Proportion (95% CI)*	
White man	24.5	Referent	1.0 (referent)
White woman	32.1	29.7 (20.8–38.5)	1.3 (0.81–1.93)
Black man	38.2	44.8 (30.6–59.2)	2.5 (1.36–4.47)
Black woman	34.8	38.1 (24.9–52.2)	1.9 (1.02–3.37)
Age ≥ 65 y	34.4	Referent	1.0 (referent)
Age < 65 y	27.0	26.9 (20.1–34.8)	0.7 (0.48–1.02)
No college education	32.4	Referent	1.0 (referent)
College education	26.8	32.4 (24.3–40.5)	1.0 (0.67–1.42)
Insured	29.0	Referent	1.0 (referent)
Uninsured	42.2	56.7 (37.2–74.3)	3.2 (1.45–7.07)
Index of Coexistent Disease score			
0 or 1 (mild)	23.0	Referent	1.0 (referent)
2 (moderate)	31.4	32.3 (23.7–43.0)	1.6 (1.04–2.53)
3 (severe)	36.2	35.0 (25.7–45.9)	1.8 (1.16–2.84)
Unmarried	33.0	Referent	1.0 (referent)
Married	27.0	28.3 (20.4–34.9)	0.8 (0.52–1.09)
No exercise	32.5	Referent	1.0 (referent)
Exercise at least once per week	21.6	22.4 (14.4–30.0)	0.6 (0.35–0.89)

* Adjusted for age, ethnicity, sex, education, lack of health insurance, Index of Coexistent Disease score, marital status, and exercise status.

RESULTS

Time of Evaluation

Thirty percent of patients were seen by a nephrologist less than 4 months before initiation of dialysis, 22% were seen 4 to 12 months before, and 48% were seen more than 1 year before (**Figure 1**). Median time from first evaluation by a nephrologist to first dialysis was 346 days.

Patient Characteristics and Time of Evaluation

Fifty-five percent of the patients were male, 27.5% were black, and 65% were younger than 65 years of age (**Table 1**). In univariate analysis, black patients ($P =$ 0.001), patients without a college education ($P < 0.001$), and patients with higher ICED scores ($P < 0.001$) were more likely to have late evaluation. Median time to evaluation was longer for white than for black patients (392 days vs. 240 days; $P < 0.001$), younger than older patients (382 days vs. 260 days; $P = 0.042$) and college-educated patients than patients with no college education (512 days vs. 256 days; $P < 0.001$). Patients with late evaluation also were significantly less likely to have received erythropoietin before initiation of dialysis ($P < 0.001$) and were less likely to have had vascular access established more than 45 days before hemodialysis ($P < 0.001$).

In multivariate analysis, black patients were more likely than white patients to be evaluated late (42.4% vs. 27.7%). In particular, black men were more likely than white men to be evaluated late (44.8% vs. 24.5%) (**Table 2**). Likewise, uninsured patients, those who did not report regular exercise, and those with greater burden and severity of comorbid disease were more likely than their counterparts to have late evaluation.

Time of Evaluation and Mortality

Median duration of follow-up was 2.2 years, during which 201 patients died. Among patients undergoing early, intermediate, or late evaluation, respectively, 80, 52, and 69 died; median follow-up was 759 days, 799 days, and 709 days; 1-year mortality rate was 4.3%, 9.5%, 13.3%; and 2-year mortality rate was 14.6%, 22.4%, and 27.6%. At 3 years, 26.3% of patients who had early evaluation, 32.7% of those who had intermediate evaluation, and 37% of those who had late evaluation had died (**Figure 2**, *top*). No evidence suggested that the proportional hazards assumption in the multivariate model had been violated (27). The bottom panel of **Figure 2** shows cumulative mortality curves for patients with diabetes.

Patients with late evaluation had a 60% greater hazard of death after adjustment for type of dialysis (**Table 3**). The hazard ratio increased slightly when demographic and socioeconomic factors (education level, group health insurance, and employment status) were added and did not change when years of smoking, exercise status, and comorbid diseases (diabetes, arrhythmia, chronic obstructive pulmonary disease, cardiovascular disease, congestive heart failure, and neoplasms) were added. When ICED score rather than comorbid disease was added, the hazard ratio for late evaluation remained similar. The hazard ratio increased when serum albumin level less than 36 g/L, hematocrit less than 0.3, and glomerular filtration rate less than

$0.07\ \text{mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$ were added to the model along with ICED score (hazard ratio, 2.3 [CI, 1.27 to 3.98]). All models showed a graded increase in hazard ratios from early to intermediate to late evaluation.

Subgroup Analyses of Time of Evaluation and Mortality

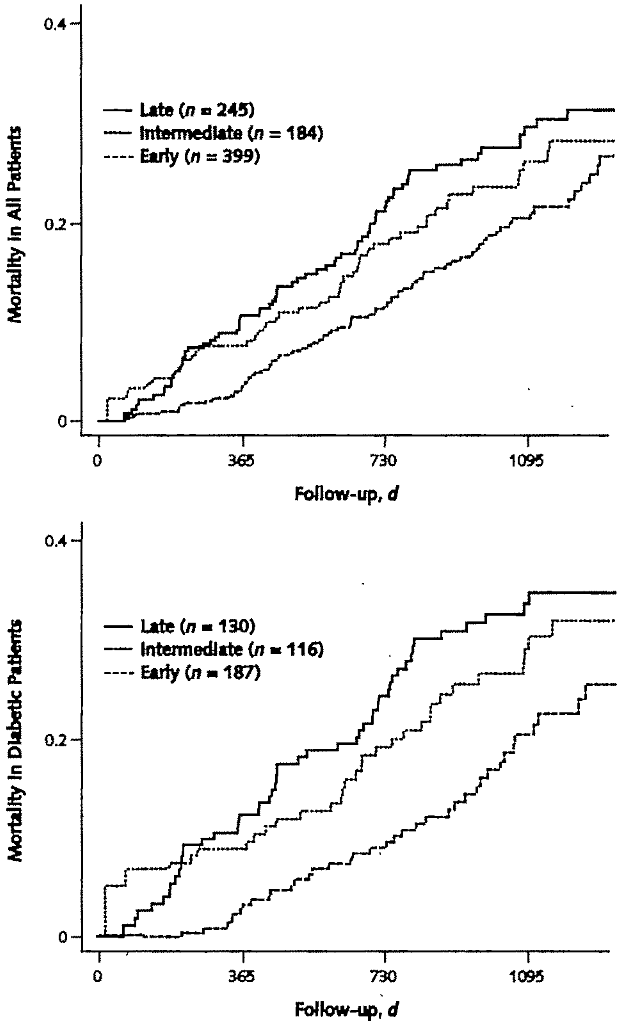
Separate regression analyses (Table 4) revealed that late evaluation was associated with greater hazard of death in diabetic patients compared with nondiabetic patients (model 4). Likewise, late evaluation was more strongly associated with death for patients with renal failure due to diabetes or hypertension than for those with renal failure due to other causes. In the sample, renal failure was due to diabetes (48.5%), hypertension (16.5%), glomerulonephritis (17.7%), and other causes (20.3%). Late evaluation was more strongly associated with death in black persons than white persons. In a 1-year analysis of a subgroup of patients whose records were reviewed for baseline type of vascular access, models with and without a variable for permanent versus temporary vascular access yielded similar hazard ratios. Permanent versus temporary access was associated with a decreased 1-year mortality rate (hazard ratio, 0.18 [CI, 0.04 to 0.85]).

Sensitivity Analyses

The graded relationship between hazard ratios and time of evaluation did not change when we redefined late evaluation as less than 1 month to less than 5 months. When less than 1 month was considered late evaluation, the hazard ratio for death among patients receiving late evaluation increased (3.0 [CI, 1.53 to 5.71]).

Kaplan–Meier estimates of mortality in patients for whom time of evaluation was missing were more similar to those observed in patients having late evaluation than in those having early evaluation. If all patients with missing time of evaluation were included with patients who had early evaluation, the hazard ratio for late evaluation in the Cox proportional hazards models (using model 5) was attenuated slightly (hazard ratio, 1.4 [CI, 0.90 to 2.15]), but the graded relationship remained.

Figure 2. **Cumulative mortality in patients undergoing early, intermediate, or late evaluation by a nephrologist.**



Top. Cumulative mortality in the total sample. Bottom. Cumulative mortality in diabetic patients.

Table 3. **Relation between Time of Evaluation and Death***

Model	Adjustment Factors	Patients, *n*	Hazard Ratio (95% CI)		
			Early Evaluation	Intermediate Evaluation	Late Evaluation
1	Time of evaluation + type of dialysis	828	1.0 (referent)	1.4 (0.92–1.99)	1.6 (1.11–2.24)
2	Model 1 factors + demographic characteristics, education level, insurance status, and employment status	718	1.0 (referent)	1.3 (0.87–2.06)	1.8 (1.21–2.61)
3	Model 2 factors + health status (years of smoking, regular exercise, and number and severity of comorbid diseases)	686	1.0 (referent)	1.2 (0.73–1.82)	1.6 (1.08–2.45)
4	Model 2 factors + health status (years of smoking, regular exercise, Index of Coexistent Disease score)	686	1.0 (referent)	1.2 (0.73–1.82)	1.6 (1.04–2.39)
5	Model 4 factors + laboratory data (serum albumin level < 36 g/L, hematocrit < 0.3, glomerular filtration rate < $0.07\ \text{mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$)	462	1.0 (referent)	1.4 (0.68–2.68)	2.3 (1.27–3.98)

* Calculated by using Cox proportional hazards regression analysis.

Table 4. **Relation between Time of Evaluation and Mortality, by Subgroups from Cox Proportional Hazards Regression Analysis**

Subgroup	Hazard Ratio (95% CI)		
	Early Evaluation	Model 4: Intermediate Evaluation*	Model 4: Late Evaluation*
All patients	1.0 (referent)	1.4 (0.92–1.99)	1.6 (1.11–2.24)
Diabetes mellitus			
Yes	1.0 (referent)	1.6 (0.84–2.94)	2.4 (1.28–4.47)
No	1.0 (referent)	0.6 (0.23–1.61)	0.9 (0.42–1.97)
Ethnicity			
White	1.0 (referent)	1.0 (0.60–1.73)	1.5 (0.92–2.37)
Black	1.0 (referent)	1.8 (0.26–12.30)	6.9 (1.07–44.71)
Attributed cause of end-stage renal disease			
Hypertension or diabetes mellitus	1.0 (referent)	1.1 (0.59–1.93)	1.99 (1.14–3.46)
Glomerulonephritis or other	1.0 (referent)	1.0 (0.35–2.63)	0.6 (0.22–1.51)
Age			
<65 y	1.0 (referent)	1.4 (0.68–2.91)	1.5 (0.82–2.87)
≥65 y	1.0 (referent)	1.0 (0.46–1.99)	1.7 (0.86–3.22)

* Model 4 included time of evaluation, type of dialysis, demographic characteristics, socioeconomic status, years of smoking, exercise status, and Index of Coexistent Disease score.

DISCUSSION

We studied a nationally representative sample of U.S. patients with incident, dialysis-dependent ESRD over a median of 2.2 years. Late evaluation of chronic kidney disease was a predictor of death after we controlled for type of dialysis, demographic characteristics, and socioeconomic factors. We also controlled for comorbid conditions by using the ICED, which reflects not only the diagnosis of at least one comorbid disease but the extent to which the disease is controlled. The ICED has been validated as a predictor of death in patients with ESRD (31). After adjustment for ICED score, the relationship between late evaluation and death was similar. Finally, when we adjusted for measures of renal function, hematocrit, and serum albumin level, the magnitude of the relationship increased. A graded relationship between timing of evaluation and mortality, in which hazard ratios increased from early to intermediate to late evaluation, was observed in all analyses.

Higher ICED scores, lower serum albumin level, and lower hematocrit were associated with late evaluation. It is possible that sicker patients are less likely to be referred (32), but delay in nephrology evaluation itself may contribute to poor health status through inattention to modifiable risk factors. For example, as renal function deteriorates, protein intake decreases (33). Patients who have late evaluation also may have less opportunity to receive appropriate nutritional counseling that would help avoid hypoalbuminemia (22). Similarly, patients who had late evaluation were less likely to have received erythropoeitin, which was associated with a lower hematocrit. Thus, a lower hematocrit may, in part, be an outcome of late evaluation. Because ICED measures the severity of comorbid disease, the higher ICED scores of patients who had late evaluation might have been decreased if earlier care had improved overall health status.

Other studies have examined whether late evaluation by a nephrologist is associated with greater mortality. One local study (11) limited to 4 months of follow-up found no statistically significant difference in mortality between patients who had late evaluation and those who had early evaluation (7% vs. 4%, respectively). A Brazilian study (14) that excluded diabetic persons found that patients with earlier diagnosis of ESRD had greater survival than patients with late diagnosis, but the adjusted hazard ratio was not statistically significant. In a single-center French study (13), multivariate analysis revealed no difference in mortality between patients who had late evaluation and those who had early evaluation. However, that sample differed from ours in that it included a smaller proportion of diabetic patients (26% versus 52% in our study) and black patients. Of note, in our subgroup analyses, the relationship between time of evaluation and mortality is largely restricted to diabetic patients. Ritz and colleagues (34) suggested that earlier evaluation by nephrologists and diabetologists may improve outcomes in patients with diabetic nephropathy. In contrast, other studies (10, 15, 16) that were also limited by number of centers or conducted outside the United States have shown an association between time of evaluation and mortality.

Our findings focus attention on the potential value of pre-ESRD care in improving outcomes of ESRD. Eknoyan and associates (35) noted that "A major determinant of poor outcomes of maintenance dialysis patients is the debilitated state of many individuals with ESRD at the time that they commence dialysis therapy." Pre-ESRD care has room for improvement. A recent study from Michigan (36) found that 73% of patients had initiation of dialysis on hospital admission and 69% used temporary vascular access. Obrador and coworkers (37) viewed the high prevalence of hypoalbuminemia and severe anemia and low levels of use of erythropoietin among U.S. patients undergoing incident dialysis as evidence of less-than-optimal pre-ESRD care.

Why are so many patients evaluated late by a nephrologist? Possible reasons include asymptomatic renal failure presenting with ESRD, noncompliance with referrals, acute renal failure, lack of access to any medical care, and the attitudes of primary care physicians about referral of patients with chronic renal insufficiency to specialists (6). We did not determine the cause of late evaluation. It should not be inferred from our data that the referral practices of primary care physicians are responsible for most late evaluations. In France, among patients who presented late, 42% had been referred but lost to follow-up, 18% were asymptomatic, and 40% had not been referred even though they had known about renal insufficiency for 2 to 11 years and were followed by a family physician (38). Campbell and colleagues (10) interviewed U.S. physicians who made late referrals. Half of the physicians discussed the need for better communication and feedback from nephrologists, about 40% feared being negatively evaluated by the nephrologist, and approximately 90% indicated that they had no training "in the timing or indications for referral of ESRD patients." New practice guidelines for the treatment of chronic kidney disease call for patients with a glomerular filtration rate less than $0.3 \text{ mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$ to be referred to a nephrologist (39). Recommendations for timing of evaluation by a nephrologist may be important on the basis of the effect on initial morbidity and length of hospital stay alone, but the additional finding that late evaluation affects mortality, particularly among diabetic patients, provides important evidence to guide clinical practice. It is not known whether care by a nephrologist compared with a non-nephrologist delays the need for dialysis. These questions and differences in mortality may be addressed in a proposed 7-year prospective study funded by the National Institutes of Health (40).

Our study has limitations. First, information on timing of nephrology evaluation was gained primarily by patient report. We attempted to verify the self-reported data by review of medical records. The median time of evaluation is similar to that seen in two studies that used medical records to determine time of evaluation (13, 20). Second, 334 patients did not respond to the question on time of evaluation. All available medical records for these patients were reviewed, and 121 of these patients were classified as having early or intermediate evaluation. A sensitivity analysis in which all patients with missing values were included as having early evaluation yielded similar results. Third, we cannot be sure that patients with acute renal failure were excluded; however, when analysis was restricted to patients in whom renal failure was attributed to diabetes or hypertension, the findings were essentially unchanged. Fourth, we have no information on frequency of visits to a nephrologist. Fifth, we cannot prove that the differences in mortality are not due to lead time bias; that is, patients who have early evaluation may start dialysis earlier in their disease than do patients with late evaluation. We attempted to account for lead time bias by including glomerular filtration rate in the final regression analysis, and the association between late evaluation and mortality remained. Mean glomerular filtration rate did not differ significantly by time of evaluation (0.070 vs. 0.073 $\text{mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$ in patients with early and late evaluation). Finally, because the patients were evaluated mainly in nonprofit settings, our results may not be generalizable to all U.S. dialysis clinics.

In summary, in a representative sample of U.S. patients undergoing incident dialysis, late evaluation for dialysis was associated with a greater burden and severity of comorbid disease, being a black man, and lack of health insurance. Late evaluation also was associated with worse survival, particularly for diabetic patients and black patients. These findings should lead to increased attention to the role of pre-ESRD care in improving outcomes of patients with ESRD.

APPENDIX

The Choices for Healthy Outcomes in Caring for ESRD is a patient outcomes research team studying dialysis care. The investigators are Neil R. Powe, MD; John Sadler, MD; Michael Klag, MD; Brad Astor, PhD; Gerard Anderson, PhD; Eric Bass, MD; William Briggs, MD; Ronald Brookmeyer, PhD; Josef Coresh, MD, PhD; Nancy Fink, MPH; Klemens Meyer, MD; Andrew Levey, MD; Nathan Levin, MD; J. Craig Longenecker, MD, PhD; Haya Rubin, MD, PhD; Paul Whelton, MD; and Albert Wu, MD, and the Clinical Liaison Committee: Thomas Depner, MD; Frederic Finkelstein, MD; H. Keith Johnson, MD; K. Shashi Kant, MD; Alan Kliger, MD; Klemens Meyer, MD; Richard Sherman, MD; Edward Schroeder, MD; Pradip Teredesai, MD; John Van Stone, MD; and Philip Zager, MD.

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ARTICLE

Sex Differences in Cardiac Catheterization after Acute Myocardial Infarction: The Role of Procedure Appropriateness

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Background: **Many studies have found that women are less likely than men to have cardiac catheterization after an acute myocardial infarction; however, it is unknown whether sex differences reflect inappropriate treatment.**

Objective: **To ascertain whether cardiac catheterization use after acute myocardial infarction in men and women varied by sex and the appropriateness of the procedure, as determined by clinical guidelines.**

Design: **Retrospective analysis of chart-abstracted data.**

Setting: **U.S. acute-care hospitals.**

Patients: **143 444 Medicare patients who were hospitalized for acute myocardial infarction between 1994 and 1996.**

Measurements: **Cardiac catheterization use within 60 days of hospitalization for acute myocardial infarction.**

Results: **Women had lower crude rates of cardiac catheterization than men (35.7% for women vs. 46.5% for men [$P < 0.001$]; difference, 10.8 percentage points). Multivariable adjustment for demographic, clinical, and hospital characteristics reduced most of the sex differences in procedure use (risk-standardized rates, 40.3% for women vs. 41.9% for men [$P < 0.001$]; difference, 1.6 percentage points). Sex differences in cardiac catheterization use varied by the appropriateness of the procedure. Risk-standardized rates of cardiac catheterization were similar for men and women with strong indications for the procedure (44.1% for women vs. 44.6% for men [$P > 0.2$]; difference, 0.5 percentage point). Rates of cardiac catheterization use among patients with weak indications did not significantly differ between men and women (16.5% for women vs. 18.0% for men [$P = 0.096$]; difference, 1.5 percentage points). Sex differences in cardiac catheterization use were largest for patients with equivocal indications (39.4% for women vs. 42.5% for men [$P < 0.001$]; difference, 3.1 percentage points).**

Conclusions: **Among elderly persons, women have lower rates of cardiac catheterization use after an acute myocardial infarction than men. However, this difference was attenuated after multivariable adjustment, and it occurred primarily in patients with equivocal indications. We found no sex variations in procedure use among patients who had strong indications for cardiac catheterization.**

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Data on sex variations in use of cardiac catheterization after an acute myocardial infarction are mixed, with some studies reporting that the procedure is used less often in women (1–13) and others finding no sex differences in use of the procedure (9, 14–19). Despite these conflicting findings, some observers have suggested that sex variations in cardiac care are evidence of sexual discrimination by physicians (20, 21) and reflect a pervasive gender bias in the health care system (22). Although studies of cardiac catheterization use have examined the effect of clinical (1–6, 8, 10, 12, 13, 23), hospital (5, 8, 13), and payer characteristics on sex differences in cardiac procedure use (1–5, 8, 10, 13), few have investigated the contribution of procedure appropriateness to sex differences in procedure use. Without considering the appropriateness of cardiac catheterization for an individual patient, it is unclear whether sex variations in cardiac catheterization use reflect proper clinical practice based on a difference of need, undertreatment of women, overtreatment of men, or a combination of factors. The few studies that have examined sex differences in cardiac catheterization use after adjusting for appropriateness of the procedure have included small numbers of patients from single centers or other selected populations and have reported conflicting results (18, 24–26). Thus, the extent to which sex differences in cardiac catheterization use after an acute myocardial infarction may be attributed to sex differences in appropriateness of the procedure is unknown.

We evaluated data from the Cooperative Cardiovascular Project (CCP), a set of medical record data abstracted for Medicare beneficiaries hospitalized with acute myocardial infarction between 1994 and 1996, to determine whether patient appropriateness for cardiac catheterization explained sex differences in procedure use. Specifically, we sought to evaluate whether sex differences in cardiac catheterization use were seen in patients with strong indications, equivocal indications, or weak indications for the procedure.

METHODS

CCP and the Study Cohort

The CCP has been described in greater detail elsewhere (27). Briefly, Medicare patients hospitalized with a primary discharge diagnosis of acute myocardial infarction (International Classification of Diseases, 9th Revision, clinical modification [ICD-9-CM], code 410.X, with the exception of readmissions code 410.X2) (28) were sampled, by state, for an 8-month period between January 1994 and February 1996. Among the 234 769 hospitalizations abstracted, we excluded patients who were younger than 65 years of age (n = 17 593), were not hospitalized with a chart-confirmed myocardial infarction (n = 31 186), or had transferred into the index hospital (n = 42 278). Pa-

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Context

Women have cardiac catheterization after an acute myocardial infarction less often than men; however, the reason—gender bias or clinical factors—is unknown.

Contribution

This large retrospective study of elderly Medicare patients compared numbers of indicated (guideline-recommended) and actual catheterizations performed within 60 days of acute myocardial infarction for women and men. Overall, women less often had cardiac catheterization than men but rates of the procedure did not differ between women and men with clear-cut guideline indications for catheterization.

Implications

Differences in catheterization use after acute myocardial infarction usually reflect appropriate clinical decisions rather than gender bias.

–The Editors

tients were sorted by admission date, and readmissions during the study period were excluded (*n* = 23 773). We also excluded patients for whom American Hospital Association (*n* = 2363), 1990 U.S. Census (*n* = 6322), or Medicare Part A (*n* = 34 187) data were not available. Finally, we excluded 1765 patients hospitalized outside of the United States, 61 patients whose race or ethnicity were unknown, and 308 patients whose mortality status was unknown at follow-up. A total of 91 325 patients met one or more of these criteria; the remaining 143 444 patients constitute the study cohort.

Appropriateness of Cardiac Catheterization

Indications for having cardiac catheterization were evaluated after the acute phase of infarction (>12 hours after symptoms onset). Using the 1996 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (29) and appropriateness criteria previously reported by Guadagnoli and colleagues (30), we classified patients into three groups (**Table 1**). The strong indication group consisted of patients in whom cardiac catheterization was generally recognized as "beneficial, useful, and effective" (ACC/AHA class I) (29). The equivocal group included patients in whom data on the effectiveness of the procedure were unclear (ACC/AHA class IIa [evidence may favor cardiac catheterization]; ACC/AHA class IIb [evidence may not favor cardiac catheterization]) or patients with uncomplicated myocardial infarctions (neither ACC/AHA class I, class II, nor class III). The weak indication group included patients who had conditions for which cardiac catheterization was considered unlikely to be effective (ACC/AHA class III). For patients who met more than one classification criterion (for example, a patient who had angina for more than 24 hours after admission and concomitant hepatic failure), classifications were prioritized by using the following order: weak indications (class III), strong indications (class I), equivocal indications (class IIa and class IIb); this was done to maximize specificity among patients classified as having a strong indication.

Cardiac Catheterization Use

The principal outcome was the use of nonacute cardiac catheterization within 60 days of hospital admission, as determined by evaluating the hospital medical record and Medicare Part A billing records for ICD-9-CM procedure codes associated with cardiac catheterization (37.22, 37.33, 88.53–88.57). We did not include cardiac catheterizations conducted within the first 12 hours of hospitalization because these were associated with the use of primary percutaneous transluminal coronary angioplasty.

Statistical Analysis

We compared men and women for differences in medical history, clinical presentation, comorbid conditions, physician, and hospital characteristics using chi-square and *t*-test analyses. We also compared men and women by the appropriateness criteria and the ACC/AHA cardiac catheterization classes used to create the appropriateness groupings.

We compared the crude rates of cardiac catheterization use for men and women in the full study cohort and when stratified by procedure appropriateness (strong, equivocal, or weak). Logistic regression models were used to derive predicted and risk-standardized rates of cardiac catheterization for men and women, adjusting for differences in sociodemographic characteristics, medical history and clinical presentation, physician characteristics, and hospital data associated with cardiac catheterization use in previous analyses (31, 32). Patient sociodemographic characteristics included race and residential ZIP code measures of median household income; distribution of occupations; and percentage of population with a high school education or higher, as reported in the 1990 U.S. Census (33). We based medical history measures on clinical experience and

Table 1. **Cardiac Catheterization Appropriateness Criteria***

Strong indications (based on ACC/AHA class I)
Angina >24 hours after admission
Ischemia observed on an exercise stress test
Reinfarction during hospitalization
Hypotension during hospitalization
Shock on admission or during hospitalization
Equivocal indications (based on ACC/AHA class IIa and class IIb)
Left ventricular ejection fraction < 0.40
Previous bypass surgery or angioplasty
Congestive heart failure or pulmonary edema on admission or during hospitalization
Non–Q-wave myocardial infarction
Weak indications (based on ACC/AHA class III)
Hepatic failure
Metastatic cancer
Terminal illness (life expectancy < 6 months)
Flexion withdrawal, decorticate, decerebate, or no motor response to cues

* Derived from ACC/AHA guidelines (29) and Guadagnoli (30). ACC/AHA = American College of Cardiology/American Heart Association.

previously identified predictors of procedure use. These measures included age, left ventricular ejection fraction, a previous myocardial infarction, congestive heart failure, smoking status, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease, dementia, functional status, and immune system status (compromised or not compromised). We also accounted for the following characteristics ascertained at admission: systolic blood pressure, heart rate, Killip class, infarct location, renal dysfunction, Q-wave infarction, ST-segment elevation, microalbuminuria, anemia, and provision of immediate reperfusion therapy (thrombolytic agents or primary percutaneous transluminal coronary angioplasy within 12 hours of admission).

Physician characteristics included age, sex, and specialty, as reported in the American Medical Association Masterfile (34). Hospital data were obtained from the 1994 American Hospital Association Survey of Hospitals (35) and included level of cardiac care facilities (none, catheterization laboratory, or coronary bypass surgery suite), ownership (public, not-for-profit, or for-profit), teaching status, number of patients with myocardial infarction who were treated, rural location (location outside of a Metropolitan Statistical Area), and U.S. Census division. To retain all variables in multivariable modeling, dummy variables were used to denote patients with missing data for left ventricular ejection fraction ($n = 52\,347$), microalbuminuria ($n = 37\,683$), weight ($n = 12\,056$), functional status ($n = 3325$), anemia ($n = 3232$), systolic blood pressure ($n = 748$), and physician characteristics ($n = 13\,177$).

Risk-standardized rates of cardiac catheterization for men and women were compared in both the overall cohort and within procedure appropriateness groups. The interaction between sex and cardiac catheterization appropriateness was confirmed by the incorporation of terms representing an interaction between patient sex and cardiac catheterization appropriateness and the use of a likelihood ratio test comparing the multivariable logistic regression model incorporating patient sex and cardiac catheterization appropriateness terms with a model that did not include these terms. To adjust for sex-associated differences in patient refusal, we repeated our analyses and evaluated the composite end point of cardiac catheterization within 60 days of hospitalization or refusal of cardiac catheterization during hospitalization. We conducted secondary analyses by further stratifying patients with equivocal indications into those who met class IIa criteria, those who met class IIb criteria, and those who did not meet class I, class II, or class III criteria. Results were adjusted for clustering of patients by hospital by using Huber–White robust estimates of standard error (36). Statistical analyses were conducted by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina) and Stata software, version 6.0 (Stata Corp., College Station, Texas); data analysis was conducted under the auspices of Qualidigm (Middletown, Connecticut), the Connecticut Peer Review Organization.

Role of the Funding Source

This article is a direct result of the Health Care Quality Improvement Program initiated by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration), which has encouraged identification of quality improvement projects derived from analysis of patterns of care; it did not require special funding on the part of this contractor.

RESULTS

Patients were predominantly white, the mean age was 77 years, and 51% of the patients were men. Compared with men, women were older and were more likely to be black and to have hypertension, diabetes, congestive heart failure, dementia, and limited functional status. However, women were less likely to have had a previous myocardial infarction or to have undergone previous cardiac procedures. Women were also more likely to have been admitted from a nursing home, more likely to have been treated at a smaller-volume hospital, and less likely to have been treated by a cardiologist or board-certified physician (**Table 2**).

Of the 143 444 patients in the study cohort, 66 691 (46.5%) had strong indications for cardiac catheterization, 67 953 (47.4%) had equivocal indications for cardiac catheterization, and 8800 (6.1%) had weak indications for cardiac catheterization. Among patients with equivocal indications, 40 693 (28.4%) met class IIa criteria; 10 868 (7.6%) met class IIb criteria; and 16 392 (11.4%) did not meet class I, class II, or class III criteria. Women were more likely than men to have strong indications for cardiac catheterization (48.4% for women vs. 44.6% for men), were less likely to have equivocal indications (45.8% for women vs. 48.9% for men), and were similar to men in the proportion of patients classified as having weak indications (5.8% for women vs. 6.5% for men) ($P = 0.001$).

Women had lower overall crude rates of cardiac catheterization than men (35.7% [CI, 35.3% to 36.0%] vs. 46.5% [CI, 46.2% to 46.9%]) ($P < 0.001$). Sex differences in crude rates of cardiac catheterization were largest among patients with equivocal indications for cardiac catheterization (34.2% in women [CI, 33.7% to 34.7%] vs. 47.5% in men [CI, 47.0% to 48.0%]) ($P = 0.001$) (**Table 3**). Among patients who had cardiac catheterization, 50.1% had strong indications, 47.4% had equivocal indications, and 2.6% had weak indications. Men who had cardiac catheterization were more likely than women to have equivocal indications for cardiac catheterization (49.9% for men vs. 44.0% for women) and less likely to have strong indications (47.3% for men vs. 53.8% for women) ($P = 0.001$).

Multivariable adjustment reduced the sex difference in cardiac catheterization use; overall risk-standardized rates of cardiac catheterization were slightly lower among women than men (40.3% in women [CI, 40.0% to 40.8%] vs. 41.9% in men [CI, 41.6% to 42.4%]) ($P < 0.001$). Sex differences in cardiac catheterization use varied

Table 2. **Patient Characteristics***

Variable	All Patients (*n* = 143 444)	Men (*n* = 72 975)	Women (*n* = 70 469)	*P* Value
Race: white/black/other, *n*	90.6/6.2/3.1	91.5/5.1/3.4	89.7/7.4/2.9	0.001
Mean age ±SD, *y*	76.5 ± 7.4	75.2 ± 6.9	78.0 ± 7.6	<0.001
Mean annual household income ±SD, *U.S. $*	30 523 ± 11 508	30 884 ± 11 686	30 192 ± 11 311	<0.001
Clinical presentation, %				
Killip class: I/II/III/IV	50/12/35/2	54/12/32/2	47/2/38/2	0.001
LVEF: unknown/<0.20/0.20–0.39/0.40–0.54/≥0.55	36/2/19/30/12	36/2/20/30/12	37/1/17/31/13	0.001
Anterior infarction	46.7	45.4	48.1	0.001
Q-wave infarction	59.7	60.2	59.2	0.001
ST-segment elevation infarction	29.2	29.6	28.8	0.001
Medical history, %				
Hypertension	61.7	55.7	67.8	0.001
Diabetes mellitus	30.6	28.2	33.2	0.001
Previous myocardial infarction	29.2	32.9	25.4	0.001
Congestive heart failure	21.5	18.4	24.8	0.001
Current smoker	14.7	16.0	13.3	0.001
Cerebrovascular disease	14.0	13.6	14.4	0.001
Peripheral vascular disease	10.7	11.6	9.8	0.001
Previous coronary artery bypass graft surgery	12.4	16.6	8.0	0.001
Previous percutaneous transluminal coronary angioplasty	6.4	7.6	5.2	0.001
Comorbid conditions, %				
Dementia	6.1	4.8	7.5	0.001
Anemia	7.1	6.3	7.9	0.001
Liver disease	0.4	0.4	0.3	0.002
Chronic obstructive pulmonary disease	20.4	22.6	18.1	0.001
Mobility: independent/assisted/unable/unknown	78/16/3/3	84/12/2/2	73/20/4/3	0.001
Urinary incontinence or anuria	7.4	5.4	9.4	0.001
Nursing facility admission	6.8	4.0	9.7	0.001
Do-not-resuscitate order before admission	9.4	6.7	12.3	0.001
Mean APACHE II score ± SD	9.8 ± 4.8	9.7 ± 4.8	9.8 ± 4.8	<0.001
Physician characteristics, %				
Race: white/black/other/unknown	54.0/1.0/12.3/32.6	53.8/1.1/12.5/32.7	54.2/0.9/12.2/32.6	0.001
Male	93.6	94.7	92.4	0.001
Board-certified	81.4	82.4	80.3	0.001
Specialty				0.001
Cardiology	30.8	33.7	27.9	
Medicine subspecialty	11.2	10.5	11.8	
Internal medicine	25.4	24.2	26.7	
Family practice	15.4	14.3	16.5	
Other	17.2	17.3	17.1	
Hospital characteristics				
Level of cardiac care facilities, %				0.001
No invasive facilities	37.8	36.9	38.7	
Catheterization available	25.7	25.3	26.2	
Coronary artery bypass graft surgery available	36.5	37.8	35.1	
Ownership: public/not-for-profit/for-profit, %	12.4/77.0/10.5	12.4/77.0/10.6	12.4/77.1/10.5	>0.2
Teaching status, %				0.024
Nonteaching hospital	66.8	66.8	66.8	
Residency or fellowship program affiliated	21.7	21.9	21.5	
Council of Teaching Hospitals hospital	11.4	11.2	11.6	
Mean acute myocardial infarction volume ± SD, *n*	171 ± 145	174 ± 148	168 ± 143	<0.001
Rural location, %	21.4	21.3	21.5	>0.2
Geographic location, %				0.001
Northeast	25.2	24.2	26.3	
South	37.1	37.2	37.0	
Midwest	21.9	21.6	22.2	
West	15.8	17.0	14.5	

*APACHE = Acute Physiology and Chronic Health Evaluation; LVEF = left ventricular ejection fraction.

on the basis of patient appropriateness for cardiac catheterization ($P < 0.001$ for the interaction between patient sex and cardiac catheterization appropriateness) (Table 3). Men and women with strong indications had identical risk-standardized rates of cardiac catheterization use (44.1% in women [CI, 43.2 to 44.9] vs. 44.6% in men [CI, 44.0 to 45.3]) ($P > 0.2$). Similarly, the difference in cardiac catheterization use between men and women with weak indications was statistically nonsignificant (16.5% in women [CI, 15.0% to 17.9%] vs. 18.0% in men [CI, 16.8% to 19.2%]) ($P = 0.096$). However, we observed modest sex differences in cardiac catheterization use among patients with equivocal indications for the procedure (39.4% in women [CI, 38.8% to 41.9%] vs. 42.5% in men [CI, 41.7% to 43.0%]) ($P < 0.001$). When patients with equivocal indications were further divided into those who met class IIa criteria; class IIb criteria; and those who did not meet class I, class II, or class III criteria, women had lower risk-standardized rates of cardiac catheterization than men, although these differences were similarly modest. Findings were similar when we evaluated the composite end point of cardiac catheterization and refusal of cardiac catheterization during hospitalization (Table 3).

DISCUSSION

Crude sex differences in cardiac catheterization use among Medicare patients after acute myocardial infarction are explained mostly by sex differences in demographic, clinical, and hospital characteristics. Residual sex differences in procedure use cannot be attributed to a broad pattern of lower rates of cardiac catheterization among women; rather, they vary by procedure appropriateness. Risk-standardized rates of cardiac catheterization use for women and men with strong indications for the procedure are similar, whereas rates were only slightly lower among women with equivocal indications. Thus, sex differences in the use of cardiac catheterization do not reflect sex-associated disparities in appropriate clinical treatment.

Earlier studies have reported conflicting findings concerning sex differences in cardiac catheterization use. Laouri and colleagues (26) reported that women were less likely to undergo "necessary" cardiac catheterization (as identified by RAND Delphi appropriateness methods) than similarly classified men (adjusted odds ratio, 0.54). The discordance between these data and our findings may reflect Laouri's study sample, which consisted of patients who had positive results on exercise stress tests; our study, on the other hand, evaluated patients hospitalized with confirmed myocardial infarction. The heterogeneity of patient ages and clinical conditions in Laouri's study sample may have increased physician uncertainty about the diagnosis of coronary disease, whereas our patients were a uniformly elderly cohort with documented disease. Socioeconomic factors may also contribute to the difference in findings. Our study included patients who had a common payer and who were drawn from a diverse spectrum of centers, whereas Laouri's study group included patients who were uninsured and were drawn primarily from public hospitals.

In contrast, both Kilaru and colleagues (18) and Wong and colleagues (25) reported no statistically significant sex differences in cardiac catheterization use after myocardial infarction and stratification of patients according to their appropriateness for the procedure. The absence of a sex difference among patients with equivocal indications in the Kilaru and Wong studies may reflect the small study samples ($n = 439$ and $n = 1133$) and centers selected for study (one public hospital in the Kilaru study and seven managed-care hospitals in the Wong study).

Our findings of similar rates of cardiac catheterization in men and women with strong indications—both for and against the procedure—are reassuring. These findings, when considered with data indicating that sex differences in cardiac catheterization use do not vary by sex of the physician (31), suggest that it is inaccurate to attribute sex differences in cardiac procedure use to gender bias by male physicians toward female patients. The large reduction in sex differences in cardiac procedure use observed after multivariable adjustment indicates that more conventional clinical characteristics may explain most of the observed variation. Sex of the patient may influence use of cardiac catheterization among patients with equivocal indications; however, because the role of cardiac catheterization in pa-

Table 3. **Crude and Risk-Standardized Rates of Cardiac Catheterization***

Variable	All Patients (n = 143 444)	Men (n = 72 975)	Women (n = 70 469)	Risk Ratio: Women/Men	P Value
	←	%	→		
Crude rate					
Overall	41.2	46.5 (46.2–46.9)	35.7 (35.3–36.0)	0.77 (0.75–0.78)	<0.001
Appropriateness					
Strong (ACC/AHA class I)	44.4	49.3 (48.8–49.9)	39.6 (39.1–40.1)	0.80 (0.79–0.82)	0.001
Equivocal	41.2	47.5 (47.0–48.0)	34.2 (33.7–34.7)	0.72 (0.71–0.73)	0.001
ACC/AHA class IIA	36.2	42.6 (41.9–43.2)	29.1 (28.4–29.7)	0.68 (0.66–0.70)	0.001
ACC/AHA class IIB	49.3	54.9 (53.6–56.3)	43.4 (42.0–44.7)	0.79 (0.76–0.82)	0.001
Not classified	48.4	54.7 (53.6–55.7)	41.0 (39.8–42.1)	0.75 (0.72–0.77)	0.001
Weak (ACC/AHA class III)	17.4	20.3 (19.1–21.4)	14.0 (12.9–15.0)	0.69 (0.63–0.76)	0.001
Risk-standardized rate					
Overall	41.2	41.9 (41.6–42.4)	40.3 (40.0–40.8)	0.96 (0.95–0.98)	<0.001
Appropriateness					
Strong (ACC/AHA class I)	44.4	44.6 (44.0–45.3)	44.1 (43.2–44.9)	0.99 (0.96–1.01)	>0.2
Equivocal	41.2	42.5 (41.7–43.0)	39.4 (38.8–41.9)	0.93 (0.91–0.95)	<0.001
ACC/AHA class IIA	36.2	37.2 (36.6–38.1)	34.6 (33.9–35.4)	0.93 (0.90–0.96)	<0.001
ACC/AHA class IIB	49.3	50.7 (48.9–52.5)	47.4 (45.3–49.4)	0.93 (0.88–0.98)	0.014
Not classified	48.4	50.2 (48.9–51.4)	45.8 (44.0–47.5)	0.91 (0.87–0.95)	<0.001
Weak (ACC/AHA class III)	17.4	18.0 (16.8–19.2)	16.5 (15.0–17.9)	0.92 (0.82–1.01)	0.096

* Reported as rates and risk ratios with 95% CIs. ACC/AHA = American College of Cardiology/American Heart Association (1996).

tients with equivocal indications is unclear, we cannot conclude that quality of care is poor on the basis of sex of the patient. Some of these patients, particularly those who meet class IIb criteria, are unlikely to obtain a benefit from cardiac catheterization that would exceed the procedure-related risks (37).

Modest sex differences in cardiac catheterization use among patients with equivocal indications suggest that sex of the patient may slightly influence physician decision making when diagnostic or therapeutic options are unclear. Women report different cardiac symptoms than men (38), and these differences in presentation may complicate decision making in the absence of definitive evidence of ischemia or reinfarction. Physicians may have lower prior estimates of the utility of cardiac catheterization in women because women have a higher comorbidity burden and because women who undergo cardiac catheterization are less likely to have evidence of coronary disease, and less severe disease, than men (39–41). The small observed difference may also reflect model misspecification or residual confounding.

Some aspects of our study merit particular attention. First, patient appropriateness for cardiac catheterization was determined by applying ACC/AHA guidelines for cardiac catheterization to data elements available in the CCP in a manner similar to that of Guadagnoli and colleagues (30). Thus, we could not identify patients who may have had a strong indication for cardiac catheterization because of a mechanical defect (for example, ventricular septal defect or left ventricle aneurysm), although we expect this to be a small population. In addition, the ACC/AHA guidelines reflect both a synthesis of professional consensus and evidence and, thus, may differ from a strict evidence-based evaluation of cardiac catheterization use. Unlike others (42), however, our purpose was not to assign patients to a definitive standard of care (for example, all patients with strong indications should have cardiac catheterization) but rather to stratify our cohort into three groups for whom the benefits of cardiac catheterization were clear, unclear, or absent according to professional practice guidelines. Because we did not have access to Medicare Part B data, we could not determine whether patients had office-based cardiac catheterizations. We relied on data obtained from a retrospective abstraction of medical records and thus may have missed undocumented clinical indications for cardiac catheterization among patients with equivocal indications. Because of the importance of clinical events that underlie indications in our study (for example, recurrent ischemia, shock, persistent angina, hepatic failure), we consider this unlikely. We evaluated Medicare fee-for-service beneficiaries who were hospitalized with myocardial infarction between 1994 and 1996, and it is unclear whether procedure appropriateness may be a factor for sex variations in cardiac catheterization use in patients younger than 65 years of age, Medicare patients enrolled in managed care plans, cardiac catheterizations not associated with myocardial infarction, or contemporary practice. Finally, the low rate of procedure use, small number of patients, and the small absolute sex difference in procedure use among patients in the weak indication group made it difficult to draw inferences about sex differences in this population.

In conclusion, our data indicate that the use of cardiac catheterization among elderly men and women hospitalized with myocardial infarction varies depending on the appropriateness of the procedure and is not likely to be attributable to gender bias. The lack of sex differences in cardiac catheterization use among patients with strong indications suggests that sex of the patient does not influence physician decision making in the presence of clear clinical evidence of the value of a procedure. However, the modest sex differences in procedure use among patients with equivocal indications suggest that sex of the patient may influence decision making, but only when treatment indications are equivocal, and even then, the effect is small.

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Smoking Status and Risk for Recurrent Coronary Events after Myocardial Infarction

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Background: **Questions remain about the importance of smoking and smoking cessation after incident myocardial infarction.**

Objective: **To assess the association between smoking status and risk for recurrent coronary events.**

Design: **Retrospective, population-based, inception cohort study.**

Setting: **Health maintenance organization from 1986 to 1996.**

Patients: **2619 persons who survived to hospital discharge after a first myocardial infarction.**

Measurements: **Relative risk (RR), assessed by using Cox proportional hazards regression analysis, for recurrent coronary events in nonsmokers (persons with no history of smoking), former smokers (persons who had stopped smoking before infarction), quitters (persons who stopped smoking after infarction), and active smokers (persons who continued smoking after infarction).**

Results: **At the time of incident infarction, 33.6% of patients were nonsmokers, 35.5% were former smokers, and 30.9% were active smokers. Of the 808 persons who were active smokers at the time of incident infarction, 449 quit smoking during hospitalization or after discharge. With nonsmokers as the reference group, the multivariable RR for recurrent coronary events (*n* = 433) was 1.17 (95% CI, 0.93 to 1.43) for former smokers and 1.51 (CI, 1.10 to 2.07) for active smokers. Among quitters, the RR decreased as duration of cessation increased: With nonsmokers as the reference group, the RR for quitters was 1.62 (CI, 1.02 to 2.61) if the duration of cessation was 0 to less than 6 months, 1.60 (CI, 0.97 to 2.60) if the duration was 6 to less than 18 months, 1.48 (CI, 0.76 to 2.51) if the duration was 18 to less than 36 months, and 1.02 (CI, 0.54 to 1.86) if the duration was 36 months or more (*P* = 0.01 for trend).**

Conclusion: **After incident myocardial infarction, smoking was associated with an elevated risk for recurrent coronary events. In persons who quit smoking after infarction, the risk declined to equal that of nonsmokers by 3 years after cessation.**

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Smoking is a risk factor for coronary artery disease (1). Among persons without coronary disease who quit smoking, the risk for incident coronary disease decreases and approaches that of nonsmokers within 2 to 3 years after cessation (2, 3). Some studies (4–17) show that quitting smoking after myocardial infarction also seems to reduce the risk for adverse outcomes, including death. However, these studies of persons with established disease generally focused on men 65 years of age or younger, had limited information about possible confounding factors, did not evaluate the time course of the potential benefits of smoking cessation, and did not compare results to those in nonsmokers. In contrast to these studies showing a benefit of smoking cessation after myocardial infarction, some evidence suggests that after infarction, smokers may not have an elevated risk for recurrent events compared with never-smokers, a finding termed the "smoker's paradox" (18–24). We examined the association between smoking status and risk for recurrent coronary events and explored the time course of potential benefits of cessation in a large population-based inception cohort of persons who survived to hospital discharge after an incident myocardial infarction.

METHODS

Setting and Participants

The study setting was Group Health Cooperative (GHC), a health maintenance organization with more than 500 000 enrollees, based in western Washington State. The organization's model of health care delivery is structured so that most routine care for enrollees, including care after myocardial infarction, is provided by personal primary care physicians. Group Health Cooperative employs more than 300 primary care physicians and contracts with more than 500 other physicians.

Eligible patients included all GHC enrollees who survived to hospital discharge after a first myocardial infarction during the period from July 1986 (women) or July 1989 (men) through December 1996. Patients with incident myocardial infarction were identified by International Classification of Diseases, 9th revision, codes from the computerized discharge abstracts of the two GHC hospitals, bills for out-of-plan services provided by non-GHC physicians and health care facilities, and Washington State death records. A trained records abstractor, assisted by study physicians, validated the incident infarctions by reviewing available inpatient medical records. Previous work (25) has confirmed the accuracy and completeness of the methods used for ascertainment of myocardial infarction.

Persons were excluded if they were younger than 30 or older than 79 years of age at the time of the incident infarction, had previously had a myocardial infarction, had the incident infarction as a result of surgery or another procedure, died before hospital discharge, or had no information available in the medical record after the incident infarction. A total of 50 patients (1.8% of the total otherwise eligible patients) were discharged alive from the hospital but had no information in the chart after the incident infarction. Persons were also excluded if they had made

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fewer than four visits to GHC or had been enrolled in GHC for less than 1 year before the incident infarction. Among persons otherwise eligible for inclusion, 9.3% were excluded because of inadequate duration of enrollment in GHC. Of the 2677 patients who were initially eligible, 58 were excluded because of indeterminate smoking status, leaving 2619 persons (97.8% of the original cohort) for analysis.

The Human Subjects Review Committees of GHC approved the study.

Smoking Status

We identified smoking status on the basis of ambulatory care and inpatient records. The GHC ambulatory medical record is an important resource because it serves as the primary method of communication among GHC physicians. It includes not only notes from ambulatory care visits but also discharge summaries of hospitalizations, results of laboratory and diagnostic tests, consultant reports, responses to annual GHC health questionnaires, and updated problem lists. Data collection included a review of the entire GHC ambulatory medical record for the period before the first infarction, the period of hospitalization associated with the incident infarction, and the period after the infarction up to a predetermined date in 1996, 1997, or 1998. Patients were classified as nonsmokers (persons with no history of smoking in the medical record), former smokers (persons who had smoked but had quit before the incident myocardial infarction), quitters (persons who were smoking at the time of the incident myocardial infarction and quit after the infarction), and active smokers (persons who were smoking at the time of the incident myocardial infarction and continued to smoke during follow-up). Only those persons who quit smoking after their incident infarction and maintained cessation for the duration of follow-up were classified as quitters. Information about the quit date, number of cigarettes smoked per day, and duration of smoking over time was also recorded. Patients were closely monitored after the incident infarction; 97.6% had a clinic visit within 3 months after hospital discharge, and the median number of visits (physician, nurse, or emergency department visits or hospitalizations) during the first year after the incident infarction was 9 (25th, 75th percentiles: 6, 14).

Clinical and Medication Covariates

Trained research assistants reviewed the ambulatory care and inpatient medical records to collect information about potential risk factors for coronary disease, such as use of health services; marital status; alcohol consumption; body weight; height; and medical conditions such as hypertension, diabetes, and congestive heart failure. Congestive heart failure was determined to have occurred on the basis of the notes of the primary care physician and consultants and the results of diagnostic tests. Hypertension was defined as pharmacologically treated hypertension; diabetes was defined as diabetes pharmacologically treated with oral hypoglycemic agents or insulin. In addition, laboratory values for random serum glucose, total cholesterol, and high-density lipoprotein cholesterol were recorded. Medication use was assessed at the time of hospital discharge after the incident infarction by using information from the discharge summary supplemented with information from the first outpatient visit and the GHC computerized pharmacy database. The status of the clinical and medication covariates was determined at the time of hospital discharge. Laboratory information was taken from the period before the incident infarction.

Background

Smoking cessation decreases the risk for myocardial infarction among people without previous coronary disease, but its effect on risk reduction after a first myocardial infarction has not been well studied.

Contribution

The researchers retrospectively observed relative risk for recurrent coronary events in patients discharged from the hospital after an incident myocardial infarction. Compared to nonsmokers, active smokers were 1.5 times more likely to have reinfarction. Among persons who had stopped smoking, relative risk decreased gradually to the nonsmokers' level over 36 months.

Implications

Physicians should emphasize the proven benefits of smoking cessation to encourage patients to quit after a first myocardial infarction.

–The Editors

End Point

The outcome of interest was recurrent coronary events, defined as nonfatal myocardial infarction or coronary death. Information on these end points was obtained from the GHC ambulatory medical record, available inpatient records, and the results of matches between Washington State death records and GHC enrollment records. In patients with established coronary disease, if the underlying cause of death was heart disease, heart failure, or arrhythmia, the death was classified as a coronary death.

Statistical Analysis

Follow-up time began at the date of discharge from the hospital after the incident infarction, and it extended to the date of the first recurrent infarction, coronary death, or censoring. Persons were censored at the date of death from causes other than heart disease, the date of unenrollment from GHC, or the end of the assigned follow-up period. Cox proportional hazards regression analysis with a time-dependent smoking status variable was used to model the association of smoking status and recurrent coronary events after adjustment for potential confounding factors (26). A patient who quit smoking during hospitalization for the

Table 1. **Characteristics of Study Patients at Time of Hospital Discharge, by Smoking Status**

Characteristic	Nonsmokers (*n* = 880)	Former Smokers* (*n* = 931)	Persons Who Quit Smoking while Hospitalized for Myocardial Infarction (*n* = 344)	Persons Who Quit Smoking after Hospital Discharge (*n* = 105)	Persons Who Continued To Smoke after Hospital Discharge (*n* = 359)
Median age (25th, 75th percentile), *y*	68.2 (58.7, 74.1)	67.6 (59.3, 73.3)	60.6 (52.4, 67.8)	60.8 (52.8, 69.0)	59.0 (49.1, 68.2)
Women, *n (%)*	412 (46.8)	251 (27.0)	148 (43.0)	48 (45.7)	129 (35.9)
Patients with congestive heart failure, *n (%)*	187 (21.3)	245 (26.3)	80 (23.2)	23 (21.9)	63 (17.5)
Patients with diabetes, *n (%)*	199 (22.6)	184 (19.8)	43 (12.5)	16 (15.2)	37 (10.3)
Patients with hypertension, *n (%)*	417 (47.4)	433 (46.5)	130 (37.8)	44 (41.9)	130 (36.2)
Patients with no alcohol consumption, *n (%)*	561 (63.8)	383 (41.1)	163 (47.4)	40 (38.1)	136 (37.9)
Median body mass index (25th, 75th percentile), *kg/m²*	26.8 (24.4, 30.6)	27.3 (24.5, 30.7)	26.6 (23.8, 30.1)	26.2 (24.1, 29.2)	26.4 (23.6, 30.1)
Median ratio of total cholesterol to high-density lipoprotein cholesterol (25th, 75th percentile)	5.5 (4.6, 6.5)	5.6 (4.6, 6.7)	5.8 (4.7, 7.0)	5.5 (4.8, 6.5)	5.8 (4.8, 7.1)
Cigarettes/d (25th, 75th percentile), *n*†	Not available	20 (20, 30)	20 (13, 30)	20 (15, 30)	20 (19, 30)
Duration of smoking (25th, 75th percentile), *y*‡	–	28 (18, 39)	37 (30, 45)	39 (30, 44)	36 (27, 45)
Patients receiving aspirin, *n (%)*	807 (91.7)	855 (91.8)	326 (94.8)	99 (94.3)	328 (91.4)
Patients receiving β-blockers, *n (%)*	456 (51.8)	466 (50.1)	167 (48.5)	49 (46.7)	172 (47.9)

* Persons who quit smoking before the incident myocardial infarction.

† Cigarettes/d is the average number of cigarettes smoked per day for persons who quit smoking before the incident myocardial infarction and the number of cigarettes smoked per day at the time of incident myocardial infarction for persons who were actively smoking at the time of incident myocardial infarction. This information was available for 544 persons (58.4%) who quit smoking before incident myocardial infarction, 303 persons (88.1%) who quit during hospitalization for incident myocardial infarction, 96 persons who quit after discharge (91.4%), and 309 persons (86.1%) who remained active smokers after incident myocardial infarction.

‡ Information on duration of smoking was available for 457 persons (49.1%) who quit smoking before incident myocardial infarction, 237 persons (68.9%) who quit during hospitalization for incident myocardial infarction, 73 persons (69.5%) who quit after discharge, and 234 persons (65.2%) who remained active smokers after incident myocardial infarction.

incident myocardial infarction was classified as a quitter. For those who quit smoking after discharge, smoking status was modeled with person-years accrued initially as if the patient were an active smoker and then after cessation as if the patient were a quitter.

To investigate the risk for recurrent coronary events in relation to the duration of smoking cessation, we divided follow-up time into four mutually exclusive categories of duration of cessation (0 to <6 months, 6 to <18 months, 18 to <36 months, and ≥36 months). Because the underlying time scale used in the regression analysis was time since hospital discharge after the first myocardial infarction, the Cox model adjusts for time since infarction, enabling an assessment of the relationship of duration of cessation independent of time since infarction. In addition, because most patients who quit smoking did so very soon after the incident infarction, time since hospital discharge and time since cessation of smoking were similar for many quitters. To help discern whether the change seen among quitters in the hazard ratio over time was due to smoking cessation rather than to any other characteristic of smokers that changed over time after discharge, we also evaluated whether the coronary event hazard ratio among active smokers varied with time since infarction.

We calculated the unadjusted rates of recurrent coronary events for each category of smoking status and used Cox proportional hazards regression analysis to compute hazard ratios of recurrent coronary events associated with smoking status after adjustment for potential confounding factors. Nonsmokers served as the reference group. Variables included in the multivariable Cox models, in addition to smoking status, were age at hospital discharge (in years); sex; body mass index (weight in kg/height in m²); alcohol consumption (none, any alcohol consumption but not physician-diagnosed alcoholism, or physician-diagnosed alcoholism); random serum glucose level; presence of congestive heart failure, hypertension, and diabetes; and use of aspirin. We examined the hazard ratio in subgroups defined by age (<65 years of age compared to ≥65 years of age), sex, presence of hypertension, presence of diabetes, body mass index (<30 compared to ≥30), thrombolytic therapy for the incident infarction, and smoking intensity at the time of the incident infarction (1 to 20 cigarettes per day compared to ≥20 cigarettes per day) using interaction terms in the Cox regression models. Analyses were done by using Stata 7.0 software (Stata Corp., College Station, Texas).

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

In the 2619 persons who survived to hospital discharge after a first myocardial infarction, the average age was 63.9 years; 37.7% of these persons were women. At the time of incident myocardial infarction, 880 patients (33.6%) were nonsmokers, 931 (35.5%) were former smokers, and 808 (30.9%) were active smokers. Of the 808 active smokers, 344 (42.6%) quit smoking during hospitalization for the incident myocardial infarction and 464 (57.4%) were active smokers at the time of hospital discharge. Of the 464 persons who were active smokers at hospital discharge, 105 quit smoking after discharge and before a recurrent event or censoring. Compared to persons who were smokers at the time of the incident myocardial infarction, nonsmokers and former smokers tended to be older, to have a greater body mass index, and to have a higher prevalence of diabetes and hypertension (Table 1). Characteristics were similar across quitter subgroups defined by duration of cessation. In the three groups with a history of smoking, the average number of cigarettes smoked per day was similar, whereas smoking duration was shorter for former smokers than for persons who quit during hospitalization or who continued to smoke.

During the 8813 person-years of follow-up (median follow-up, 3.0 years), 433 recurrent coronary events occurred: 272 nonfatal myocardial infarctions, 94 fatal myocardial infarctions, and 67 other coronary deaths. A total of 229 patients were censored because they were lost to follow-up; they represented 390 years or 4.2% of total person time. The proportion of person time lost to follow-up was similar across smoking status: 4.5% among nonsmokers, 3.7% among former smokers, 5.2% among quitters, and 3.6% among active smokers. With nonsmokers as the reference group (Table 2), the hazard ratio of recurrent coronary events was elevated among those who quit smoking after incident myocardial infarction (adjusted relative risk, 1.43 [95% CI, 1.07 to 1.93]) and those who continued to smoke (adjusted relative risk, 1.51 [CI, 1.10 to 2.07]). The risk for recurrent coronary events was similar in those who quit before the incident myocardial infarction and in nonsmokers. The hazard ratio associated with smoking status and recurrent coronary events did not differ across subgroups defined by sex, age, hypertension, diabetes, body mass index, thrombolytic therapy, or smoking intensity. In sensitivity analyses, further adjustment for family history of coronary heart disease; ratio of total cholesterol to high-density lipoprotein cholesterol; pulse rate; serum creatinine level; thrombolytic therapy for the incident infarction; education; marital status; calendar year; and use of β-blockers, angiotensin-converting enzyme inhibitors, or lipid-lowering therapy at hospital discharge changed the hazard ratio estimates associated with smoking status only slightly. Adjustment for these covariates not included in the final model typically changed the estimates by less than 5% and never by more than 10%. Confidence intervals also changed only slightly, and the statistical significance of the associations did not change. For example, adjustment for the aforementioned additional covariates resulted in a range of hazard ratios of 1.42 to 1.45 among quitters and 1.50 to 1.54 among active smokers.

Among persons who quit smoking after the incident myocardial infarction compared to nonsmokers, the hazard ratio declined as the duration of cessation increased, and it approached that of nonsmokers after 3 years (test for trend, $P = 0.01$ among persons who quit after infarction) (Table 3). By contrast, the hazard ratio among active smokers compared to nonsmokers did not decline over time since infarction. We detected no differences across subgroups defined by sex, age, hypertension, diabetes, body mass index, or smoking intensity in the association between decreasing hazard ratio and increasing duration of cessation.

DISCUSSION

In our study, persons who continued to smoke after incident myocardial infarction had a 50% increase in risk for recurrent coronary events compared to nonsmokers, an excess risk apparent across demographic, clinical, and treatment subgroups. Among those who quit smoking after incident myocardial infarction, the risk seemed to decline over time until it matched that of nonsmokers as the duration of cessation approached 3 years. Former smokers (persons who had quit smoking before the incident myocardial infarction) did not seem to have an elevated risk compared to nonsmokers.

The elevated risk for recurrent coronary events among active smokers after incident myocardial infarction is of considerable public health importance. Active smokers made up nearly 20% of our cohort, and this proportion is similar to that found in other populations with prevalent heart disease (27, 28). The magnitude of the increased risk among smokers in our study is similar to that found in other investigations of populations with prevalent disease that have found smokers to have elevated risk compared to

Table 2. **Unadjusted Rate and Multivariable-Adjusted Hazard Ratio of Recurrent Coronary Heart Disease Events, by Smoking Status**

Smoking Status	Coronary Heart Disease Events, *n*	Person-Years at Risk	Unadjusted Rate per 1000 Person-Years	Multivariable-Adjusted Hazard Ratio (95% CI)*
Nonsmokers	139	3084	45.1	1.00 (reference)
Persons who quit smoking before incident myocardial infarction	162	2970	54.5	1.17 (0.93–1.49)
Persons who quit smoking after incident myocardial infarction	72	1502	47.9	1.43 (1.07–1.93)
Active smokers after incident myocardial infarction	60	1257	47.7	1.51 (1.10–2.07)

* After adjustment for age, sex, presence of congestive heart failure, presence of diabetes, presence of hypertension, aspirin use, alcohol use, body mass index, random serum glucose level, and time from hospital discharge.

Table 3. **Duration of Smoking Cessation and Unadjusted Rate and Multivariable-Adjusted Hazard Ratio of Recurrent Coronary Heart Disease Events**

Smoking Status	Coronary Heart Disease Events, *n*	Person-Years at Risk*	Unadjusted Rate per 1000 Person-Years	Multivariable-Adjusted Hazard Ratio (95% CI)†
Nonsmokers	139	3084	45.1	1.00 (reference)
Persons who quit smoking after incident myocardial infarction				
Duration of cessation				
0 to <6 months	23	186	123.7	1.62 (1.02–2.61)
6 to <18 months	21	418	50.3	1.60 (0.97–2.60)
18 to <36 months	15	434	34.5	1.48 (0.76–2.51)
≥36 months	13	464	28.0	1.02 (0.54–1.86)
Active smokers after incident myocardial infarction	60	1257	47.7	1.51 (1.10–2.07)

* Total number of persons still under observation over time among those who quit smoking after incident myocardial infarction was 449 at 0 to <6 months, 414 at 6 to <18 months, 349 at 18 to <36 months, and 226 at ≥36 months.

† After adjustment for age, sex, presence of congestive heart failure, presence of diabetes, presence of hypertension, aspirin use, alcohol use, body mass index, random serum glucose level, and time from hospital discharge.

nonsmokers (29–31). We found no evidence to support the previously reported "smoker's paradox" among those who continued to smoke after infarction, even among those who received thrombolytic therapy (32, 33). Given the considerably younger age of smokers at the time of the incident infarction and their elevated risk after infarction, smoking seems to have a consistently adverse effect on health.

As in other studies of postinfarction populations or populations having procedures for coronary artery disease (5, 30, 31, 34), approximately half of persons classified as smokers at the time of their coronary event or procedure permanently quit smoking; this finding underscores the strong motivating influence of myocardial infarction in achieving cessation (35). Those who quit smoking after their incident infarction had an overall risk for recurrent events that was similar to that of active smokers; however, the risk decreased over time and approached that of nonsmokers 3 years after cessation, a result consistent with the time course of benefit in the primary prevention setting (2, 3). Given this time-dependent association, the overall risk observed among quitters is in part a function of the length of follow-up. Thus, the overall risk evident among quitters in our analysis (median follow-up, 3 years) is probably an overestimate because average survival after hospital discharge substantially exceeds the length of follow-up time in our cohort (36).

Various factors may explain the time lag for decreased risk among quitters after incident infarction. Although smoking acutely potentiates thrombosis by producing oxidative stress, endothelial dysfunction, and platelet activation (37, 38), it may also promote atherosclerosis and thrombosis by longer-term means that include impaired insulin sensitivity and renal dysfunction (39, 40). Alternatively, some persons who quit smoking after myocardial infarction may have quit in part because of more (unmeasured) smoking-related symptoms and thus may have been sicker than those who continued to smoke (41). These persons would presumably have recurrent events sooner rather than later after cessation.

Our study has limitations. We defined smoking status on the basis of retrospective chart review that relied on physician assessment and documentation of smoking status. Smoking status was therefore not prospectively and systematically assessed or recorded. This limitation should be placed in the context of the postinfarction setting, where patients were followed closely and clinical attention would probably be directed toward minimizing modifiable potential risk factors, such as smoking. Smoking status was based on patient report as documented in the medical record and was not verified by biochemical assay; among those with heart disease, however, self-report seems to be reasonably accurate (4, 42). Given the relationships observed, misclassification of smoking status would probably have attenuated the true association between active smoking and risk for recurrent coronary event; thus, our findings may underestimate the risk associated with smoking. In addition, we were able to classify as quitters only those who had permanently quit smoking; those who quit and then resumed smoking were classified as active smokers.

Although the relations seen persisted in numerous sensitivity analyses, we cannot exclude the possibility of confounding (for example, confounding due to income level). In particular, persons who are able to quit smoking may be more compliant than others, and patient adherence is known to be related to improved prognosis (43). In addition, we could not adjust for the individual physician. It is possible that physicians who were better able to assist patients with cessation might also have provided other beneficial care that reduced the risk for recurrent coronary events and was not accounted for in the models. However, adjustment for other measures that might be associated with physician practice, such as use of medications (including β-blocker, lipid-lowering, and angiotensin-converting enzyme inhibitor therapies) did not alter the associations with smoking status. Moreover, unlike most treatments, smoking cessation is a complex process that is partly determined by patient characteristics (such as "readiness to quit") rather than physician-initiated care. Finally, we could not assess for the possibility of variance inflation due to clustering by physician. However, because there are many physicians relative to the number of patients, the variance inflation due to clustering is probably small, unless there was a high degree of variation of outcomes across physicians. This study also has many strengths: Our findings compare the various clinical groups of smokers (nonsmokers, former smokers, quitters, and active smokers) and are derived from a large, population-based cohort with information available on a broad range of important clinical, treatment, and laboratory variables.

In conclusion, smoking after incident myocardial infarction was associated with an increased risk for recurrent coronary events. However, in persons who quit smoking after the incident myocardial infarction, the risk seemed to decline to equal that of nonsmokers after 3 years of cessation. These results, taken together with the increasing array of behavioral and pharmacological therapies that help persons achieve and maintain smoking cessation (44), the safety of these interventions in those with coronary disease (45–47), and the strong motivating influence of infarction (35), support efforts to make smoking cessation an important goal for patients and physicians after myocardial infarction.

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Torsade de Pointes Associated with Very-High-Dose Methadone

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Background: **Methadone is an effective treatment for opioid dependency and chronic pain. A methadone derivative, levacetylmethadol, was withdrawn from the European market after being associated with torsade de pointes. To date, no association between methadone and this arrhythmia has been described.**

Objective: **To evaluate a series of methadone-treated patients experiencing torsade de pointes.**

Design: **Retrospective case series.**

Setting: **Methadone maintenance treatment programs in the United States and a pain management center in Canada.**

Patients: **17 methadone-treated patients who developed torsade de pointes.**

Measurements: **Chart review for concomitant arrhythmia risk factors and quantification of corrected QT interval (QTc).**

Results: **The mean daily methadone dose was 397 ± 283 mg, and the mean QTc interval was 615 ± 77 msec. Fourteen patients had a predisposing risk factor for arrhythmia. A cardiac defibrillator or pacemaker was placed in 14 patients; all 17 patients survived.**

Conclusions: **This series raises concern that very-high-dose methadone may be associated with torsade de pointes. Given the likely expansion of methadone treatment into primary care, further investigation of these findings is warranted.**

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Methadone, a synthetic opioid, has been successfully used for more than 35 years to treat heroin addiction; as a component of methadone maintenance treatment, it is prescribed daily to approximately 180 000 Americans (1). Methadone is also an effective and inexpensive therapy for chronic pain (2). In heroin-abusing patients, high-dose methadone (>60 mg/d) has shown greater efficacy in reducing illicit drug use than has lower-dose therapy (20 mg/d) (3). A national survey recently confirmed that higher doses of methadone are now being used: From 1988 to 1995, the average dose increased from 45 to 59 mg/d (4).

Currently, the U.S. Food and Drug Administration is no longer involved in direct oversight of methadone maintenance treatment, and the Center for Substance Abuse Treatment has recommended expanding access to treatment by shifting opioid-dependent patients to primary care, office-based practice (5). Levacetylmethadol, a derivative of methadone, is the only other approved therapy for opioid-dependent patients in the United States. Recently, the European Agency for the Evaluation of Medicinal Products withdrew levacetylmethadol from the market after noting an association with seven cases of torsade de pointes, a potentially fatal ventricular arrhythmia (6). In the United States, five such cases have been reported to the manufacturer of levacetylmethadol, and one case report has been published (7). To date, no such association has been described with methadone. We report 17 cases of torsade de pointes in patients receiving very high doses of methadone.

METHODS

Patients and Setting

Cases were observed in two clinical settings from 1996 to 2001. Nine cases were reported from methadone maintenance treatment programs for opioid addiction in the United States, and 8 cases were reported from a chronic pain clinic in Alberta, Canada. The connection between cases was made solely as a result of communication between two physicians after 6 cases of torsade de pointes in methadone-treated patients from Denver, Colorado, aroused concern.

We did not formally attempt to identify patients by review of databases or medical records or by active case solicitation. We excluded 3 patients: 1 patient receiving methadone maintenance treatment who experienced torsade de pointes (excluded because of previous diagnosis of congenital long-QT syndrome) and 2 patients treated with methadone for chronic pain who died suddenly (excluded because of inadequate documentation of arrhythmia). We ascertained patient survival data through communication with primary care providers.

Definitions

All cases required the presence of a prolonged QT segment, with a corrected QT interval (QTc interval) of at least 500 msec in the setting of polymorphic ventricular tachycardia (8). We used Bazett's formula to determine the QTc interval: QTc interval = QT interval (in msec) divided by the square root of the preceding R-R interval (in sec) (9). All patients were assessed by echocardiography or angiography, or both, for the presence of structural heart disease, defined as left or right ventricular systolic dysfunction. Serum electrolyte levels measured at the time of presentation were reviewed. Hypokalemia was defined as a serum potassium level less than 3.5 mmol/L (3.5 mEq/L). Medications, alcohol, or illicit substances that may have contributed to this arrhythmia were tabulated for all patients. Medications were considered to be potential contributing factors if review of manufacturer labeling or a literature search revealed a clinical or experimental association with QT prolongation or torsade de pointes. In addition, drugs that may have inhibited the metabolism of

Context

Several drugs, including antiarrhythmic agents, antihistamines, and tricyclic antidepressants, can cause acquired long-QT syndrome (torsades de pointes).

Contribution

This case series describes 17 patients who had torsades de pointes while taking very high doses of methadone for chronic pain or methadone maintenance. The average daily methadone dose was about 400 mg. Fourteen of the patients had known risk factors for arrhythmia, such as hypokalemia, or were taking other drugs that could prolong the QT interval.

Cautions

These data suggest, but do not prove, that very-high-dose methadone can cause torsades de pointes.

–The Editors

methadone were tabulated. Particular attention was given to screening for antihistamines, macrolide and fluoroquinolone antibiotics, imidazole antifungal agents, antimalarial agents, phenothiazines, and tricyclic antidepressants.

RESULTS

We documented 17 cases of torsade de pointes in methadone-treated patients. The **Table** summarizes the patients' clinical characteristics. The mean age (±SD) of the patients was 49 ± 9 years; 10 of the 17 patients were female. Each patient experienced overt syncope during arrhythmia documentation. The mean daily methadone dose was 397 ± 283 mg. The mean QTc interval on presentation was 615 ± 77 msec; the mean heart rate was 64 ± 15 beats/min, and 10 patients were bradycardic (≤60 beats/min). Seven patients had hypokalemia, and 1 patient had hypomagnesemia on presentation. Nine patients were receiving a potentially QT-prolonging drug, and 1 patient was taking a medication known to inhibit the metabolism of methadone. Only 3 patients were found to have structural heart disease. Overall, 14 of 17 patients had at least one potential risk factor for arrhythmia. Of note, 5 patients being treated for chronic pain were receiving the antiepileptic drug gabapentin. Six patients had had their methadone dose increased within 1 month before presentation with torsade de pointes, and 7 had been receiving methadone therapy for 3 or fewer months. An implantable cardiac defibrillator or pacemaker was placed in 14 patients; all 17 patients survived.

DISCUSSION

This series raises concern about a possible association between very-high-dose methadone and torsade de pointes. The clinical characteristics of patients in this series typify most cases of drug-induced torsade de pointes, which are characterized by a relative absence of structural heart disease, by associated hypokalemia, and by a female predominance (10, 11). A noteworthy finding was that 6 patients had had an increase in methadone dose in the month just before presentation. Although 2 patients who died suddenly were excluded from analysis, they had also begun receiving substantially higher methadone doses 48 hours before their death. A previous study (12) showed a similar

Table. **Clinical Characteristics of the Patients**

Patient	Sex	Age	Dose	Treatment Duration	Corrected QT Interval	Contributing Drugs	Potassium Level[*]	Structural Heart Disease
		y	*mg/d*	*mo*	*msec*		*mmol/L*	
1[†]	M	50	1000	>12	600	Olanzapine	4.1	No
2[†]	M	52	550	9	625	None	4.6	No
3	M	60	97	>12	560	None	4.3	No
4	F	51	90	4	585	Cocaine	(3.2)	Yes
5[†]	F	45	85	3	590	Alcohol	4.1	No
6	F	46	126	6	500	Alcohol, fluoxetine	(2.3)	No
7	M	38	300	>12	700	Fluoxetine, levacetylmethadol	4.0	No
8	M	51	110	>12	570	Nelfinavir	4.1	No
9	F	47	65	2	540	Olanzapine, alcohol	(3.0)	No
10	F	52	650	11	785	None	4.1[‡]	Yes
11	F	43	600	6	765	Olanzapine	4.6	No
12[†]	F	41	660	<1	611	Fluoxetine	(3.3)	No
13	F	55	270	1	600	None	(3.2)	No
14	F	33	680	10	625	None	3.6	Yes
15[†]	M	52	540	1	650	Amitriptyline	(3.4)	No
16[†]	M	47	600	<1	635	None	4.2	No
17	F	75	330	3	522	None	(3.3)	No
Mean ± SD		49 ± 9	397 ± 283		615 ± 77			

[*] Serum potassium levels below the reference range (<3.5) are noted in parentheses.

[†] Patients who had an increase in methadone dose within 1 month of arrhythmia presentation.

[‡] This patient had a low serum magnesium level—0.68 mmol/L (reference range, 0.70 to 1.00 mmol/L).

temporal association between malignant arrhythmia onset and an escalating dose of cisapride.

Another consideration in evaluating drug-induced torsade de pointes is the effect of metabolic inhibitors on serum drug concentration. Methadone is metabolized primarily via the hepatic cytochrome P450 isoenzyme CYP3A4 (13). In one case in our series, therapy with nelfinavir, a potent inhibitor of CYP3A4, was initiated just before the development of torsade de pointes. This type of drug–drug interaction leading to torsade de pointes is well documented for cisapride and the antihistamine terfenadine (12, 14).

Two potential pathophysiologic mechanisms might explain an association between methadone and torsade de pointes. One possibility is that synthetic opioids mediate this arrhythmia through bradycardia. Drug-induced torsade de pointes is generally a pause-dependent arrhythmia, usually occurring at slow heart rates (15, 16). Both methadone and its derivative levacetylmethadol have demonstrated negative chronotropic effects in vitro (17). The bradycardia seen in most patients in this series suggests that methadone may have facilitated torsade de pointes through these effects. Another possibility is that methadone may lead to this arrhythmia through prolongation of cardiac action potential duration by delaying repolarization. This mechanism underlies most cases of drug-induced QT prolongation and torsade de pointes, and it frequently occurs through inhibition of the rapidly activating component of the delayed rectifier potassium ion current (I_{kr}) (10). Experiments using the whole-cell patch-clamp technique have recently shown that methadone diminishes this current in vitro (18). An electrocardiographic study demonstrating an 8% absolute increase in the QTc interval after methadone initiation corroborates this in vitro mechanism (19).

Our report has many limitations. The sample size is small, and in the absence of a control group, we cannot make definitive statements about a true causal association. Moreover, we did not conduct genetic testing of individuals for congenital long-QT syndrome. Baseline electrocardiographic data were not available because, unlike with levacetylmethadol, the manufacturer of methadone does not require this screening before initiation of methadone therapy. In addition, because cases were discovered fortuitously, we cannot estimate the actual incidence of torsade de pointes in methadone-treated patients. Although patients are monitored closely in both methadone maintenance treatment programs and the chronic pain clinic, other cases may have been missed. An under-reporting bias might exist in the methadone maintenance treatment population, where it may be assumed that sudden death is the result of narcotic overdose.

In summary, the characteristics of patients in this series are consistent with most cases of drug-induced torsade de pointes, in which a confluence of factors is implicated in arrhythmia development. An association between methadone and torsade de pointes seems plausible in light of cases observed with the chemically similar compound levacetylmethadol, as well as the in vitro and electrocardiographic evidence suggesting that methadone delays cardiac repolarization. However, our report should not be interpreted to suggest that high-dose methadone cannot be used safely. The mean methadone dose associated with arrhythmia in this series was substantially higher than doses typically encountered in clinical practice. For instance, the average methadone dose in Colorado's 1400 actively treated patients in 1999 was 68 mg/d, and although doses greater than 100 mg/d were prescribed for 22% of patients, fewer than 0.1% of patients received doses greater than 300 mg/d (Colorado Department of Human Services, Alcohol and Drug Abuse Division, May 1999). In contrast, the chronic pain clinic in this report tended to use substantially higher doses: In approximately 130 actively treated patients, the average dose was 300 mg/d. Nevertheless, physicians involved in methadone maintenance treatment and chronic pain management should be aware of a potential association between very-high-dose methadone and torsade de pointes, particularly in the setting of additional arrhythmia risk factors. Because methadone treatment will probably expand into the realm of the general internist, further studies appear to be warranted.

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The In-Training Examination in Internal Medicine: An Analysis of Resident Performance over Time

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Background: **The In-Training Examination in Internal Medicine (IM-ITE) has been offered annually to all trainees in U.S. medical residency programs since 1988. Its purpose is to provide residents and program directors with an objective assessment of each resident's personal performance on a written, multiple-choice examination and the performance of the residency program compared with that of its peers.**

Objective: **To analyze trends in the demographic characteristics and scores of examinees during the first 12 years of administration of this examination.**

Design: **Descriptive analysis over time.**

Setting: **U.S. residency programs in internal medicine, 1988–2000.**

Participants: **Residents at all levels of training in categorical, primary care, and medicine–pediatrics programs in the United States and Canada. The number of examinees increased from 7500 in 1988 to almost 18 000 in 2000.**

Measurements: **After calibration of the scores for each examination, test results were compared and analyzed for selected cohorts of residents over 12 years.**

Results: **More than 80% of residents in medicine training programs participate in the IM-ITE, most on an annual basis throughout their period of training. Test performance improves at a predictable rate with each year of training. Since 1995, international medical school graduates have persistently outperformed graduates of U.S. medical schools. Test results were affected by the timing of the examination, the time that was available to complete the examination, and the actual time that residents spent in internal medicine training before each examination.**

Conclusions: **The IM-ITE scores generally improve with year of training time spent in internal medicine training before the examination and time permitted to complete the examination. These observations provide evidence that the IM-ITE is a valid measure of knowledge acquired during internal medicine training.**

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The In-Training Examination in Internal Medicine (IM-ITE) was first administered in 1988. It was developed to serve as a self-evaluation instrument for internal medicine housestaff at the midpoint of their residency training. Since its introduction, the IM-ITE has been administered annually to residents on a voluntary basis. Now, more than 395 residency training programs in the United States, 13 programs in Canada, and 9 programs in Puerto Rico participate in the examination. Most residency training programs offer the examination for postgraduate year (PGY) 1 residents and PGY3 residents in addition to PGY2 residents. In the 1999–2000 academic year, almost 18 000 residents took the examination; this included more than 80% of the residents enrolled in internal medicine programs in the United States.

This report reviews the demographic characteristics of the trainees who have participated in the IM-ITE over the past 12 years and analyzes trends in test results. It builds on data first presented in 1994 that reviewed trends during the first 6 years of testing (1), provides insights into the effect of changes in housestaff composition on performances in the examination over time, and analyzes the effect of changes in test administration on examination scores.

BACKGROUND

The IM-ITE was developed in the late 1980s and was first administered in 1988 as a cooperative effort of the American College of Physicians (now the American College of Physicians–American Society of Internal Medicine [ACP–ASIM]), the Association of Program Directors in Internal Medicine (APDIM), and the Association of Professors of Medicine (APM) (1). The examination is intended to be used solely as an educational resource. It provides residents with a measure of their knowledge in general internal medicine and its subspecialties compared with that of their peers nationwide. It also provides program directors with an assessment of their own residents and compares the overall performance of their program by level of training to the performance of a national cohort. Results on the IM-ITE are not meant to be used as criteria for promotion or termination within a residency program or to determine eligibility for participation in the certification examination of the American Board of Internal Medicine. Furthermore, it is specifically stated in each examination booklet that the results of the IM-ITE should not be used by outside regulatory agencies to measure the knowledge of individual residents or the quality of individual training programs (1).

The examination tests the knowledge base of PGY2 residents, although residents at all levels of training now participate in the examination on an annual basis. Each examination is prepared by a committee composed of three representatives from each of the sponsoring societies and a chairperson appointed by the ACP–ASIM. The committee members serve staggered terms of 3 years each to maintain a high level of continuity in the examination from year to year. Committee members have expertise in the fields of general internal medicine and each of the subspecialties of internal medicine.

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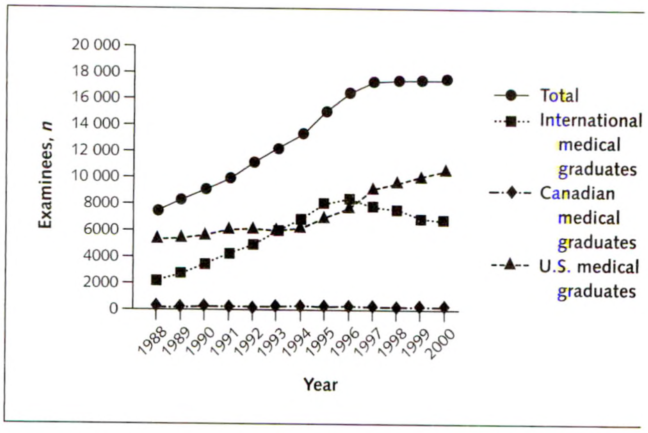
Figure 1. **Number of examinees by country of medical school training, 1988–2000.**



The total number of persons taking the examination (*circles*) is shown, as well as the number of examinees according to region of medical school training—United States (*triangles*), Canada (*diamonds*), or international (non–U.S. or Canada) (*squares*).

Preparation of questions for the examination begins 1.5 years before the administration date. The content of the examination is driven by a blueprint that allocates approximately 20% of test items to general internal medicine and 7% to 15% to each subspecialty. Questions are designed to test the residents' knowledge of physical examination skills, diagnostic acumen, and appropriate therapy. (For sample questions, see Appendix, available at www.annals.org.) The examination emphasizes items that involve synthesis and judgment rather than simple recall. To increase reliability, 25% to 50% of questions are selected from examinations given 2 or more years previously on the basis of their content and performance characteristics. New questions are written, edited, and reviewed by the examination committee. The examination consists of 350 to 375 test items. Before 1995, the examination was administered in two sessions of 3 hours each; in 1995, the time for each session was increased to 3.5 hours.

Test booklets are prepared by the ACP–ASIM and distributed to the testing site of each participating residency program. Program directors are responsible for administering the test, including proctoring, maintaining security, reporting irregularities, and returning materials to the National Board of Medical Examiners (NBME) for scoring. Before 1999, the examination had been administered in January. However, since the 1999–2000 academic year, the examination is administered in October, 3 months earlier, to obtain results earlier in the year for each cohort of residents and to avoid interference with resident recruitment.

The NBME statistically analyzes the performance characteristics of each question on the IM-ITE. Questions that are answered correctly by fewer than 30% of residents and those that fail to discriminate high-scoring from low-scoring examinees are closely reviewed by the committee chairperson to determine whether results of that item should be included in the overall test score. In addition, each year the performances of the total test and each subspecialty section are analyzed for their quality and internal consistency. The precision of scores for the total examination, as measured by the Kuder–Richardson reliability coefficient (KR_{20}) (2), is consistently at a level similar to that found in national certifying examinations and state licensing tests ($KR_{20} > 90$).

Each resident receives a report that compares his or her overall score with that of a national cohort of peers at the same level of training. Residents also receive scores on each subspecialty section of the examination and a listing of educational objectives for questions answered incorrectly. Program directors receive copies of the individual reports for each of their residents and composite scores of their residents by level of training compared with those of their peers for the total examination and each of its subsections.

METHODS

This report reviews trends in the performance characteristics of annual examinations from 1988 to 2000 (the 1999–2000 academic year). For this study, numeric data, demographic characteristics, and test scores for each annual examination were calculated and analyzed. Results from each examination were calibrated by using the Rasch model (3). The calibration procedure estimates the difficulty of each examination item independently of examinee proficiency. Conversely, examinee proficiencies are estimated independently of item difficulty. The examinees' proficiencies for each year were equated and placed on a common scale. In this study, scores were equated to a baseline benchmark score (±SD) of 500 ± 100 for PGY2 residents who took the 1988 examination. This allowed direct comparison of test difficulty and examinee performance across the 12 years of our analysis.

RESULTS

Program Participation

Country of Medical School Training

The number of residents participating in the IM-ITE increased from 7537 in 1988 to 17 883 in 1999–2000. This number plateaued over the last 4 years of the analysis, reflecting participation by more than 80% of the total residents in internal medicine training programs in the United States (**Figure 1**). Over the 12-year period analyzed, the number of residents who graduated from U.S. medical schools increased steadily. Included in the group of U.S. medical school graduates are residents who graduated from U.S. schools of osteopathic medicine. Their numbers increased from 374 in 1989 to 850 in 1999–2000. Each year, osteopathic medical school graduates have represented 4% to 5% of the examinees. The number of graduates from international programs taking the examination increased rapidly from 1988 to 1996 and tailed off for the last 4 years of the analysis. From 1994 to 1996, the numbers of international graduates who took the examination exceeded the number of U.S. graduates. In the 1999–2000 examination, approximately 60% of examinees were U.S. medical school graduates and 40% were international medical school graduates. The number of graduates from Canadian medical schools participating in the examination increased slightly from 184 in 1988 to 368 in 1999–2000, peaking at 429 in 1996.

Type of Training Program

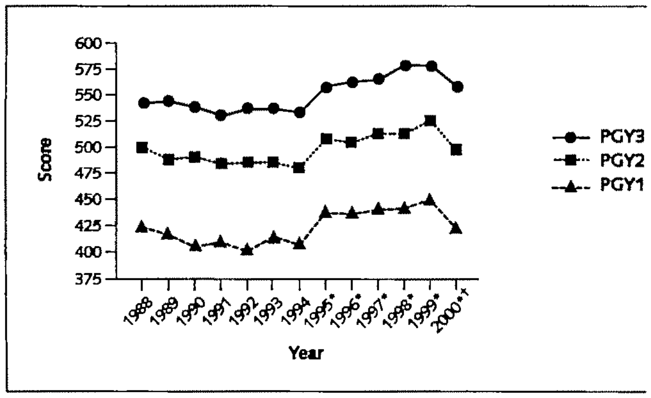
Most housestaff taking the IM-ITE are enrolled in categorical programs. The numbers of residents in categorical programs increased from 4175 in 1988 to 13 642 in 1999–2000, reflecting the increased participation of categorical programs in the examination process in the United States. The number of residents from primary care general internal medicine programs decreased from 1988 to 1994 and recovered in the last four examinations of our analysis; in 1999–2000, 2126 primary care residents took the IM-ITE. The greatest increase in participation over the 12-year period was seen among medicine–pediatrics residents, whose numbers increased fivefold, from 253 in 1988 to 1269 in 1999–2000. Also of note, the number of residents (PGY1) in preliminary medicine programs taking the examination increased over the 12-year period, reflecting the increased participation of PGY1 housestaff overall in the examination; in 1999–2000, 511 interns in preliminary medicine programs took the examination.

Test Results

PGY Levels

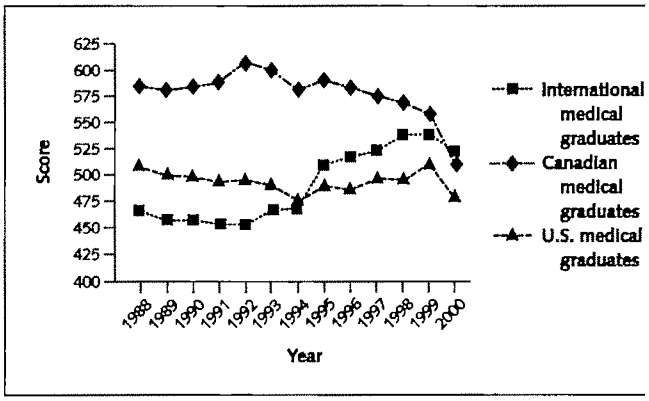
Figure 2 shows annual examination scores from 1988 to 2000 for residents at the PGY1, PGY2, and PGY3 levels. As expected, on every examination, PGY3 residents outperformed PGY2 residents, who outperformed PGY1 residents. The relative difference in scores between PGY3 and PGY2 residents on each examination is between 40 and 60 points (approximately 0.5 SD); the relative difference between PGY2 and PGY1 residents on each examination is between 70 and 80 points (approximately 0.75 SD).

Figure 2. **Mean scores per year, 1988–2000, of examinees by year of postgraduate year of training.**



*Duration of examination increased from 6 to 7 hours. †Examination administered in October instead of January. PGY1 = postgraduate year 1; PGY2 = postgraduate year 2; PGY3 = postgraduate year 3.

Figure 3. **Mean examination scores per year, 1988–2000, according to country of medical school training.**



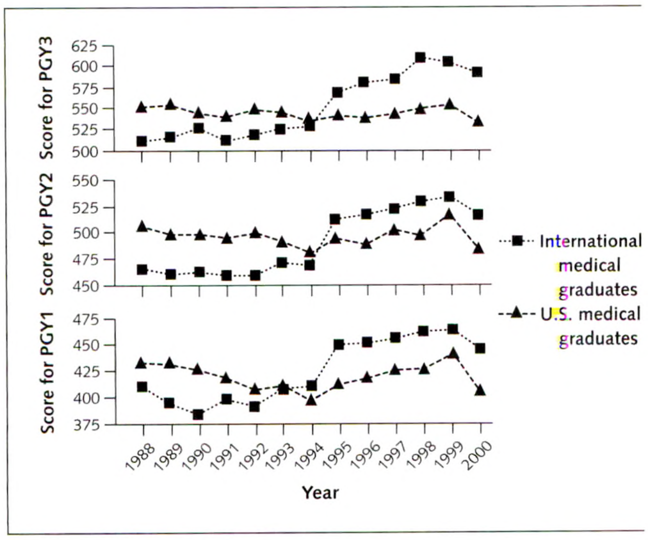
Shown are the scores for graduates of U.S. medical schools (*triangles*), Canadian medical schools (*diamonds*), and international (non–U.S. or Canadian) medical schools (*squares*).

For the first 6 years, the performance of residents at each level of training was consistent, with a slight downward trend. In 1995, however, there was a striking increase in scores in all PGY levels that persisted until 1999–2000. Of note, in 1995 the time allowed to complete the examination was increased from 6 to 7 hours, and this seems to explain the improvement in performance. The decline in performances in the 1999–2000 examination relates to the date of test administration. The 1999–2000 examination was administered in October 1999; this was 3 months earlier in the academic year than all previous examinations, which had been administered in January. The differences in scores for the PGY1 and PGY2 cohorts who took the examination in January 1999 and again 9 months later in October 1999 as PGY2 and PGY3 residents were three quarters of that which might have been anticipated on the basis of performances by residents at these levels of training on previous examinations.

Country of Medical School Training

For the first 7 years that the examination was administered, graduates of U.S. medical schools consistently scored higher than graduates of international medical schools (**Figure 3**). Since 1995, international graduates consistently outperformed U.S. graduates on each examination and scored highest of all cohorts on the most recent examination. We observed the most dramatic increase in scores among international graduates in 1995, when their average total score rose by almost 50 points (0.5 SD), probably because of the extra time allotted for completion of the examination. Graduates of Canadian medical schools have scored strikingly higher than either group on all examinations except in the 1999–2000 academic year.

Figure 4. **Mean examination scores, 1988–2000, for graduates of U.S. medical schools (*circles*) and for graduates of international (non–U.S.) medical schools (*squares*).**



Top. Examinees in postgraduate year 3 (*PGY3*) of U.S. residency training. **Middle.** Examinees in postgraduate year 2 (*PGY2*) of U.S. residency training. **Bottom.** Examinees in postgraduate year 1 (*PGY1*) of U.S. residency training.

The likelihood that the improved performance by international graduates on the 1995 examination and on subsequent examinations was related to the increased time for completion of the examination is substantiated by the observation that marked increases in scores for international graduates were noted for all three PGY levels in the same year (**Figure** 4). Because this occurred in a single year (rather than sequentially over 3 years), the improvement is probably explained by an external factor, such as the time allotted for completion of the examination, rather than a greater proficiency among the international medical school graduates (which would have been reflected in a 3-year trend, as the cohort progressed from PGY1 to PGY3). This interpretation is further verified by an observed 44-point increase from the 1994 to 1995 examination scores among residents who reported that English was not their native language, compared with a 13-point increase in the scores of native English speakers (data not shown). On all examinations before 1995, native English speakers outscored non–native English speakers; on all subsequent examinations, residents for whom English was not their primary language outscored their English-speaking counterparts.

Since 1995, graduates from international medical schools have scored higher than graduates from U.S. medical schools on every examination at every PGY level. For the cohorts of interns who began their training in 1996, 1997, or 1998, PGY1 graduates of international medical schools consistently scored higher than their U.S.-trained counterparts. Between PGY1 and PGY2, cohorts of international medical school graduates and U.S. medical school graduates improved their performance by approximately 75 points on subsequent examinations. Between PGY2 and PGY3, the magnitude of improvement for international graduates continued at the same pace; however, the increased score of U.S. graduates amounted to only two thirds of the anticipated score (**Figure** 5).

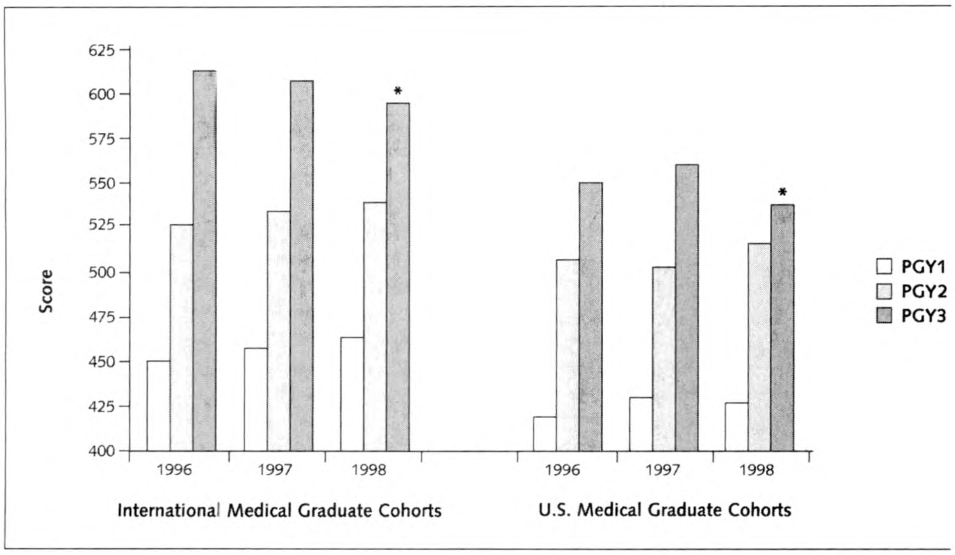
Type of Training Program

The average scores of residents who were enrolled in residency programs for primary care internal medicine were similar to those of residents enrolled in categorical programs. This observation held true for interns in their first year of testing and for residents in their PGY2 and PGY3 years for all examinations. However, the average scores of residents enrolled in medicine–pediatrics programs or preliminary medicine (internship) programs were significantly lower than those of residents enrolled in categorical or primary care programs. It should be noted that training in medicine–pediatrics is 4 years, with 2 years in medicine and 2 years in pediatrics; thus, during each year of training, medicine–pediatrics residents spend approximately half of their time, on average, on medicine rotations. When examined 6 months into their internship, the average scores of medicine–pediatrics PGY1s were 20 to 25 points lower than those of interns who graduated from U.S. medical schools and were enrolled in categorical or primary care programs. For a given cohort of medicine–pediatrics residents, the average increase of scores from PGY1 to PGY2, from PGY2 to PGY3, and from PGY3 to PGY4 was 50 points annually compared with an average annual increase of 75 points in the scores of U.S. and international medical school graduates in internal medicine and primary care programs between PGY1 and PGY2 and for international graduates between PGY2 and PGY3. Thus, the increases in total score between PGY1 and graduation were between 130 and 150 points for all groups (data not shown). After 4 years of training, the residents in medicine–pediatrics programs scored only slightly below the levels of U.S. medical school graduates completing categorical or primary care programs.

DISCUSSION

The IM-ITE is a resource for residents to compare their knowledge with that of their peers. The scores of residents on the IM-ITE have been shown by others to correlate closely with the pass–fail results on the certifying examination of the American Board of Internal Medicine (4–7). Indeed, the IM-ITE is a useful tool for gauging the readiness of a resident to perform well on that examination. The IM-ITE is also a useful measure for annually assessing the rate of improvement of a resident's knowledge during his or her housestaff training. It is a method to evaluate "work in progress." However, absolute scores on the examination are affected by nuances in the test administration. Results are affected by the timing of the examination and the time available to complete the exam, as well

Figure 5. **Comparison of scores on consecutive annual examinations between international medical graduates and U.S. medical school graduates who began their training in 1996, 1997, or 1998.**



In each cohort (based on year in which training began—1996, 1997, or 1998), resident performance on the examination is shown by training year (postgraduate year 1, 2, or 3 [*PGY1, PGY2, PGY3*]). *Examination was administered in October instead of January.

as the actual time that residents spend in internal medicine training experiences before taking the examination.

The IM-ITE provides residents and program directors with a snapshot of a resident's knowledge as assessed by a written examination at specific points of time during residency training. The examination is reliable, accurate, and internally consistent ($KR_{20} = 0.94$). Now that it has been equated to a target reference point, annual examinations may be compared and analyzed to determine trends over time and to assess improvements in the performances of specific cohorts of residents. For instance, the average score on the examination for a given cohort of residents increases by 75 points between years of training. Increases in scores in this range were noted for almost all cohorts of U.S. and international medical school graduates from categorical and primary care programs between PGY1 and PGY2 and for international medical school graduates between PGY2 and PGY3. The relative decline in performance improvement for U.S. graduates between PGY2 and PGY3 is not easy to explain; possible explanations include complacency or lack of effort by PGY3 graduates of U.S. medical schools; excessive time moonlighting (8); better preparation by international graduates; or some other, as-yet unknown reason.

The striking increase in scores on the examination for residents at all levels of training in 1995 is probably related to the increased time allotted for completion of the examination. This improvement in performance occurred almost exclusively in international graduates; in particular, it occurred in residents for whom English was not their native language. The IM-ITE was never intended to be a "speed" examination—that is, an examination in which residents are tested not only for their knowledge but also for their ability to complete the test in a prescribed time. However, previous analysis has shown that performance on items that appeared toward the end of the test booklet for each section failed to discriminate persons with high scores from those with low scores. By increasing the time for completion of the test, this problem was solved, and the examination performance improved accordingly for non-native English-speaking international graduates.

The across-the-board decreases in scores in the 1999–2000 examination for all PGY levels are probably related to the timing of this examination. All previous examinations had been administered in January, giving a consistent 12-month period between examinations. The 1999–2000 examination was administered 3 months earlier, in October. As a result, the interexamination in-training time for PGY2 and PGY3 residents was reduced from 12 to 9 months after their previous examination, and PGY1 housestaff were tested 3 months, rather than 6 months, into their internship. On this examination, there was a decrease between the observed and expected scores of approximately 25% at all levels of training. Upper-level medicine–pediatrics residents were affected most by the change in the timing of the examination because their in-training time in internal medicine rotations was on average only 4.5 months between the 1999 examination and the 1999–2000 examination.

For all examinations, the magnitude of improvement between examinations was less for medicine–pediatrics residents than for residents in categorical or primary care programs. This is probably related to the fact that medicine–pediatrics residents devote, on average, only half of their time each year to training in internal medicine. The scores for medicine–pediatrics residents increased an average of

50 points per year, compared with an average of 75 points per year seen in cohorts of residents in other programs. The improvement in test scores over the 4 years of training by medicine–pediatrics residents is only slightly below that observed for cohorts of U.S. graduates in categorical or primary care programs over their 3 years of training.

Residents and program directors find the IM-ITE extremely valuable (1). Residents use their results to identify their areas of relative proficiency and deficiency as they prepare for the certifying examination of the American Board of Internal Medicine. Program directors use the results of the examination to counsel low-scoring residents and to rearrange rotations or set up self-study programs to meet the unique needs of individual residents. However, the IM-ITE does not discriminate "good" residents from "bad" residents or "good" physicians from "bad" physicians. In fact, program directors, supervising residents, and the individual residents have difficulty correlating the scores on the IM-ITE or other in-training examinations with ward or clinic performances (9–11). The IM-ITE is not a substitute for evaluating skills that can be assessed only by direct observation. It is only one measure, albeit a very useful measure, for evaluating the improvement in a resident's base of knowledge over time (12).

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Is Volume Related to Outcome in Health Care? A Systematic Review and Methodologic Critique of the Literature

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Purpose: To systematically review the methodologic rigor of the research on volume and outcomes and to summarize the magnitude and significance of the association between them.

Data Sources: The authors searched MEDLINE from January 1980 to December 2000 for English-language, population-based studies examining the independent relationship between hospital or physician volume and clinical outcomes. Bibliographies were reviewed to identify other articles of interest, and experts were contacted about missing or unpublished studies.

Study Selection: Of 272 studies reviewed, 135 met inclusion criteria and covered 27 procedures and clinical conditions.

Data Extraction: Two investigators independently reviewed each article, using a standard form to abstract information on key study characteristics and results.

Data Synthesis: The methodologic rigor of the primary studies varied. Few studies used clinical data for risk adjustment or examined effects of hospital and physician volume simultaneously. Overall, 71% of all studies of hospital volume and 69% of studies of physician volume reported statistically significant associations between higher volume and better outcomes. The strongest associations were found for AIDS treatment and for surgery on pancreatic cancer, esophageal cancer, abdominal aortic aneurysms, and pediatric cardiac problems (a median of 3.3 to 13 excess deaths per 100 cases were attributed to low volume). Although statistically significant, the volume–outcome relationship for coronary artery bypass surgery, coronary angioplasty, carotid endarterectomy, other cancer surgery, and orthopedic procedures was of much smaller magnitude. Hospital volume–outcome studies that performed risk adjustment by using clinical data were less likely to report significant associations than were studies that adjusted for risk by using administrative data.

Conclusions: High volume is associated with better outcomes across a wide range of procedures and conditions, but the magnitude of the association varies greatly. The clinical and policy significance of these findings is complicated by the methodologic shortcomings of many studies. Differences in case mix and processes of care between high- and low-volume providers may explain part of the observed relationship between volume and outcome.

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Measuring and understanding the association between volume and outcome in the delivery of health services has been the focus of much research since the 1980s (1, 2). Recently, purchasers and consumer groups have taken an interest in the wider public dissemination of data on hospital volume for specific surgical procedures and medical conditions (3–5). Because high volume has been associated with better health outcomes for a variety of procedures and conditions, these groups recommend that consumers or health plans use data on volume to choose high-quality hospitals and physicians. Because reliable, valid, and timely information about health outcomes is lacking, data on volume are even more attractive. The wisdom of this policy, however, depends critically on the strength, magnitude, and meaning of the association between volume and outcome in health care.

During the past 20 years, a large body of research has focused on measuring and explaining the association between patient outcomes and the volume of health services provided by hospitals and physicians (1, 2, 6–11). Many (but not all) studies have documented that higher volume is associated with better outcomes. Two principal hypotheses have been advanced to explain these relationships: 1) Physicians (and hospitals) develop more effective skills if they treat more patients ("practice makes perfect") or 2) physicians (and hospitals) achieving better outcomes receive more referrals and thus accrue larger volumes ("selective referral") (2, 6, 9, 10).

Past reviews of this subject have focused only on specific procedures or conditions (12–14) or on effects of hospital volume (12, 15), have included non–population-based studies (14–16), or were done before many recent primary studies (12, 16). In addition, to our knowledge, no comprehensive review has systematically analyzed and described the methodologic rigor of this literature. This project was undertaken to address some of these limitations as part of a 2000 joint workshop of the U.S. Institute of Medicine and the National Cancer Policy Board (17). We set out to conduct a systematic review of the research evidence linking volume and outcome in health care, to summarize and describe the methodologic rigor of the existing literature, and to highlight the research and policy implications of these findings.

METHODS

Study Identification and Selection

We searched MEDLINE for English-language articles published between 1 January 1980 and 31 December 2000 that assessed the relationship between volume and outcome in health care. Our search algorithms combined the Medical Subject Headings (MeSH terms) and text words *outcome, outcome assessment, outcome and process assessment, volume, utilization, frequency, statistics,* and *regionalization* with names of clinical conditions and procedures (Appendix). Bibliographies were reviewed to identify other articles of interest, and experts were contacted about missed or unpublished studies. We also searched the Cochrane Collaboration database.

For our systematic review, we selected English-language articles in which hospital or physician volume was an independent variable, health outcomes (for example, death, stroke, or clinical complications) were the dependent variable, samples were community- or population-based, and patients had primarily been treated since 1980. When multiple articles used the same data, we included the most recent or complete article. We excluded studies published before 1980 because clinical and surgical care and outcomes have changed considerably since then for nearly all of the topics we reviewed. We excluded studies from single institutions, voluntary registries, or other convenience samples because of concerns about reporting bias and generalizability.

Our initial search also identified articles about volume and outcome in trauma, newborn intensive care, and organ transplantation. We did not include these topics in our review because these services have already been extensively regionalized or are otherwise highly regulated by government or other administrative bodies.

Review Methods

Two of the authors reviewed each article independently, using a standardized abstraction form to record study characteristics, methodologic attributes, and research results. Reviewers were not blinded to journal, authors, or findings. The degree of initial agreement between reviewers was very high ($\kappa = 0.82$ to 1.0). Any discrepancies were resolved by discussion. A third reviewer was used in rare instances when the original two reviewers did not reach full agreement. We critically read each study with an eye toward assessing its methodologic rigor as well as describing its results.

Our methodologic review focused on key design attributes that influence the validity and generalizability of systematic reviews and the studies on which they are based (18, 19). Some preexisting patient factors, such as disease severity and burden of comorbid illness, are clear determinants of outcome independent of volume. Because it is necessary to account for differences in such factors to make valid comparisons between high- and low-volume providers, we assessed the quality of risk-adjustment techniques (12, 14, 20). We considered four levels of risk adjustment (none, models based on administrative data alone, models that included some clinical data, and clinical models with good calibration [Hosmer–Lemeshow test]) and discrimination (c-statistic $\geq$ 0.75) (20). In addition, we noted whether the investigators controlled for any specific processes of care (medical therapies, surgical techniques, or adjunctive procedures) that are known to result in better outcomes. Increasing evidence shows that high-volume providers may more consistently use proven effective therapies, such as aspirin or β-blockers in myocardial infarction (21) or adjuvant therapy in breast cancer (22). We also noted whether the investigators had explicitly measured the appropriateness of patient selection for procedural conditions. Although there has been little investigation of this issue, one study of carotid endarterectomy found that high-volume surgeons had a higher proportion of operations for inappropriate indications compared with low-volume surgeons (23).

We ascertained four other analytic attributes: the type of outcomes assessed, the number of hospitals and physicians in each study (an indicator of the potential for variation at the two provider levels of interest), the number of volume strata examined, and the unit of analysis (whether effects of hospital and physician volume were assessed). Finally, samples that included all patients undergoing a specific procedure were considered more generalizable to the overall population than studies restricted to patients with one type of insurance.

Statistical Analysis

Studies that found a statistically significant mortality advantage for high-volume providers ($P < 0.05$) were considered positive. For each study, we recorded the definition of high and low volume (cases per year) and the overall mortality rate of the sample. All summary death rates reflect in-hospital mortality unless otherwise specified. We calculated the absolute difference in mortality rate between the highest and lowest volume strata reported and expressed this as the number of excess deaths per 100 cases attributable to low volume. We report medians and ranges for high- and low-volume thresholds, mean mortality rates, and absolute differences in mortality rates. A few studies assessed volume as a continuous variable, making it impossible to calculate a mortality difference between high- and low-volume providers. We included data on whether these studies demonstrated statistically significant associations in our summary. We used chi-square tests to assess associations between positive findings and methodologic attributes. All analyses were done by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Methodologic Characteristics of Included Studies

Our systematic review identified 254 articles. Eighteen articles reported on more than one procedure or condition. Because we summarized the literature by topic, we evaluated each article that studied more than one procedure as more than one study. We reviewed a total of 272 studies, of which 135 (53%) met all inclusion criteria. These 135 studies covered 27 clinical topics. Studies were most commonly excluded because volume was not an independent variable ($n = 43$), the sample was not population based ($n = 40$), or the study data were obtained before 1980 ($n = 29$). Studies were also excluded if no primary health outcomes were assessed, if mixed outcomes were assessed (for example, death plus long length of stay), or if data were duplicative.

We found the literature to be extremely heterogeneous, even for a given procedure, making formal meta-analysis impossible. The methodologic characteristics of the 135 studies we reviewed are described in Table 1. Overall, 124 studies were from the United States, 6 were from Canada, 3 were from Europe, and 2 were from the United Kingdom. Half of all the studies we identified were published since 1998, underscoring the growing interest in this topic. The vast majority of reports were based on state or national hospital-discharge databases and had sample sizes that exceeded 1000 and included 20 or more hospitals and 50 or more physicians. For 79% of studies, the primary outcome was death, usually inpatient death. Many studies, however, reported 30-day mortality rates, and several articles on cancer reported long-term survival. Twenty-one percent of studies measured more than just death. For example, all 12 studies of coronary angioplasty also reported rates of emergency coronary artery bypass surgery, and half of the investigations of carotid endarterectomy reported stroke or other neurologic outcomes. Ninety percent of studies analyzed at least three categories of volume, usually tertiles or quartiles, and a few analyzed volume (or the logarithm of volume) as a continuous variable.

Among the 135 studies we reviewed, 124 attempted to detect the effects of hospital volume on outcome and 45 compared the influence of physician volume. Most individual studies were one-dimensional, examining hospital volume only (67%) or physician volume only (8%). Nine percent of studies examined both hospital and physician volume but failed to explore joint effects. Only 16% of studies performed multivariate analyses designed to separate the independent or synergistic effects of hospital and physician volume on outcomes.

We were particularly interested in the type of risk-adjustment techniques used, if any. Failure to account for imbalances in patient case mix among providers can seriously confound the relationship between volume and outcome. Twelve percent of studies performed no risk adjustment. Most studies (60%) used administrative data to adjust for some combination of age, sex, and discharge diagnoses. Approximately one in four studies (28%) used clinical data in their risk-adjustment models. Among this group, only 10 studies (7%) reported risk-adjustment models that were robustly discriminating and well calibrated.

Two other, higher-level methodologic issues were rarely addressed. Only two studies (23, 24) measured the appropriateness of patient selection. Ten investigators tried to account for differential use of key processes of care between high- and low-volume providers. Five studies of cancer (22, 25–28) adjusted for use of adjuvant therapy or type of surgical resection. Three studies of coronary angioplasty controlled for use of key pharmacologic therapies (heparin, aspirin, or β-blockers) (29, 30) or adjunctive procedures (intra-aortic balloon pump or stents) (29, 31). In a study of myocardial infarction, Thiemann and colleagues (21) adjusted for use of aspirin, β-blockers, and revascularization. Espehaug and colleagues (32), who studied total hip replacement, adjusted for prosthesis type and use of perioperative antibiotics.

Table 1. **Methodologic Characteristics of Reviewed Studies (n = 135)**

Characteristic	Value, %
Sample size ≥ 1000 persons	82
Sample representative of overall population	64
Number of hospitals or physicians studied	
<20 hospitals and <50 physicians	6
≥20 hospitals or ≥50 physicians	7
≥20 hospitals and ≥50 physicians	87
Type of primary outcome	
Death	79
Other clinical outcomes with or without death	21
Volume analyzed by >2 categories	90
Unit of analysis	
Hospital or physician volume	75
Hospital and physician volume analyzed separately	9
Hospital and physician volume analyzed simultaneously	16
Type of risk adjustment	
None	13
Administrative data	60
Clinical data	20
Clinical data with robust prediction model	7
Appropriateness of patient selection measured	2
Clinical processes of care measured	7

Summary Findings of Included Studies

Of the 135 studies we reviewed, 90 examined hospital volume only, 11 focused on physician volume only, and 34 assessed both. Overall, there were 169 assessments of the relationship between hospital or physician volume and outcomes. One hundred and eighteen comparisons (70% of the total) indicated a statistically significant association between higher hospital or physician volume and better health outcomes. No study documented a statistically significant association between higher volume and poorer outcomes. Overall, the same proportion of studies reported significant associations between outcomes and hospital volume (71%) and between outcomes and physician volume (69%). Of the 21 studies that examined the independent effects of both physician and hospital volume, 12 found significant independent effects for both, 4 found significant independent effects for hospital volume only, 4 found significant independent effects for physician volume only, and one found such effects for neither.

We did not find a simple relationship between the quality of risk adjustment and research results. A positive relationship between hospital volume and outcome was reported in 44% of articles with no risk adjustment, 82% of those with risk adjustment based on administrative data, and 50% of those with risk adjustment based on clinical data ($P < 0.001$). We found a positive association between physician volume and outcome in 62% of studies with no risk adjustment, 68% of those with risk adjustment using administrative data, and 73% of investigations using clinical risk-adjustment models ($P > 0.2$). Reports published in general medical or medical journals were more likely to support a relationship between hospital volume and outcome than were those published in surgical journals (86% vs. 52%, respectively; $P < 0.001$). No such relationship with publication type was found for studies of physician volume and outcome. We found no associations between research findings and other methodologic characteristics, such as sample size, number of providers, representativeness, type of outcome, number of volume strata, measurement of processes of care, or year of publication.

Although the evidence supported the general proposition that higher volume is associated with better outcomes, the consistency and magnitude of the relationships varied greatly. **Tables 2** and **3** summarize by topic the characteristics and findings of the effects of hospital and physician volume. We found the most consistent and striking absolute differences in mortality rates between high- and low-volume hospitals for pancreatic cancer surgery (median difference, 13 deaths per 100 cases), esophageal cancer surgery (12 deaths per 100 cases), pediatric cardiac surgery (11 deaths per 100 cases), treatment of AIDS (9.3 deaths per 100 cases), and surgery for unruptured abdominal aortic aneurysm (3.3 deaths per 100 cases). Evidence to support a relationship between hospital volume and outcome was much more limited and inconsistent for many other common surgical procedures and conditions. For procedures such as coronary artery bypass grafting (CABG) and coronary angioplasty, the median difference in mortality rates between high- and low-volume centers was 1.6 and 0.2 per 100 cases, respectively. **Tables 2** and **3** report the absolute mortality rates for each condition so that the magnitude of the volume effect can be compared with the underlying adverse event rate.

Among the smaller subset of investigations of relationships between physician volume and outcome, the most striking differences in mortality rates between high- and low-volume surgeons were seen for pancreatic cancer, ruptured abdominal aortic aneurysm, and pediatric cardiac surgery (median differences of 3 to 14 deaths per 100 cases for the three procedures). Surgeon volume seemed to be a more important determinant of outcomes than hospital volume in the case of CABG, carotid endarterectomy, surgery for ruptured abdominal aortic aneurysm, and surgery for colorectal cancer.

DISCUSSION

Our systematic review of the past 20 years of research on the relationship between volume and outcome evaluated 135 population-based studies involving 27 procedures and clinical conditions. The methodologic rigor of published studies was very heterogeneous and was modest overall. Most articles examined effects of hospital volume or physician volume only. Very few sought to identify the simultaneous contribution of hospital and physician volume to outcomes. The quality of risk-adjustment techniques also varied; only one in four studies used clinical data for risk adjustment, and fewer reported robust risk models. The limitations of using administrative information for risk adjustment are beyond the scope of our discussion but have been reviewed extensively elsewhere (20).

We found that 71% of all studies of hospital volume and 69% of studies of physician volume reported a statistically significant association between higher volume and better health outcomes. No study documented a statistically significant association between higher volume and worse outcomes. We are confident that the overall association between hospital volume and outcome is robust. However, studies that performed more methodologically sophisticated risk adjustment using clinical data were less likely to report a positive effect of hospital volume on outcome than were studies that did not adjust for risk or used administrative data to do so. It is therefore possible that subtle differences in disease severity or comorbidity may partly explain the association between hospital volume and outcome. We found no pattern of less impressive results in higher-quality studies in the less extensive literature examining the relationship between physician volume and outcomes.

The magnitude of the volume–outcome association varied greatly by topic. We found the most consistent and striking differences in mortality rates between high- and low-volume providers for several high-risk procedures and conditions, including pancreatic cancer, esophageal cancer, abdominal aortic aneurysms, pediatric cardiac problems, and treatment of AIDS. The magnitude of volume–outcome relationships for more common procedures, such as CABG, coronary angioplasty, and carotid endarterectomy, for which selective referral and regionalization policies have been proposed, was much more modest. This was true even after we took the lower average mortality rates for these procedures into account.

This systematic review confirms and extends the findings of earlier work. Previous reviews have also found that the associations between procedure volume and surgery outcomes are strongest for pancreatic and esophageal cancer and are more modest or heterogeneous for most other conditions (12, 13, 15, 16). Our approach to research synthesis differed because we sought to comprehensively review the methodologic rigor and findings of a large number of procedures and conditions, focus on population-based studies (to increase generalizability), and estimate a summary effect of hospital and physician volume across studies for each topic.

Although the literature generally supports the notion that high volume is often associated with better outcomes, many questions remain about the clinical and policy significance of these relationships. The relative contribution of hospital versus physician volume is largely unknown because very few studies have examined both types of volume

Table 2. **Summary of Articles Examining Associations between Hospital Volume and Death***

Procedure or Condition (Reference)	Studies Included	Studies with Significant Volume–Outcome Association	Range of Time Periods Studied	Median Cases per Year Defining Low Volume (Range)†	Median Cases per Year Defining High Volume (Range)†	Median Average Mortality Rate (Range)	Median Absolute Difference in Mortality Rate for High vs. Low Volume (Range)
	n			*n*		%	
AIDS (38–43)	6	6	1984 to 1994	1 (1 to 160)	100 (5 to 161)	17.3 (9.0 to 25.2)	9.3 (3.7 to 20.1)
Myocardial infarction (21, 37)	2	2	1980 to 1995	73‡	238‡	13.8 and 15.2§	2.3§‖
Coronary angioplasty (31, 34, 44–50)¶	9	5	1989 to 1997	200 (46 to 200)	400 (160 to 1000)	1.4 (0.9 to 2.9)	0.2 (0.0 to 1.4)
Coronary artery bypass surgery (33, 37, 51–56)	8	6	1980 to 1995	100 (35 to 224)	500 (96 to 1421)	4.1 (2.8 to 6.5)	1.6 (0 to 4.4)
Pediatric cardiac surgery (56–58)	3	3	1988 to 1995	19 (10 to 100)	300 (100 to 400)	7.3 (6.8 to 7.7)	11.0 (2.3 to 15.5)
Carotid endarterectomy (24, 35, 59–71)§	15	7	1980 to 1997	10 (5 to 50)	50 (21 to 100)	1.8 (0.9 to 2.3)	0.4 (−0.5 to 1.8)**
Surgery for unruptured abdominal aortic aneurysm (56, 65, 67, 72–76)	8	7	1980 to 1997	12 (3 to 31)	36 (12 to 433)	7.5 (3.8 to 7.6)	3.3 (1.1 to 11.6)
Surgery to repair ruptured abdominal aortic aneurysm (67, 72–78)	8	2	1980 to 1995	9 (2 to 10)	20 (5 to 50)	49.8 (40.0 to 63.2)	7.9 (1.5 to 18.7)
Lower-extremity arterial bypass surgery (65, 67)	2	1	1982 to 1997	13 and 20	32 and 100	3.1 and 3.8	1.1 and 1.4
Pancreatic cancer surgery (79–88)	10	9	1984 to 1997	5 (1 to 22)	20 (3 to 200)	9.7 (5.8 to 12.9)	13.0 (3.0 to 17.9)
Esophageal cancer surgery (79, 89, 90)	3	3	1984 to 1997	5 (5 to 10)	30 (11 to 200)	13.9 (8.9 to 14.0)	12.0 (11.0 to 13.9)
Breast cancer surgery (25)	1	1	1984 to 1989	10	151	NA	††
Colorectal cancer surgery (26–28, 52, 54, 65, 89, 91–93)	10	4	1983 to 1997	18 (10 to 84)	115 (18 to 253)	6.0 (3.5 to 12.3)	1.9 (−1.2 to 9.7)**
Lung cancer surgery (65, 79, 93, 94)	4	2	1983 to 1997	7 (5 to 37)	19 (11 to 170)	5.5 (1.9 to 12.9)	1.9 (1.6 to 3.9)
Gastric cancer surgery (52, 89, 93)	3	1	1986 to 1997	10 (5 to 15)	63 (15 to 201)	10.9 (6.2 to 12.2)	6.5 (4.0 to 7.1)
Total hip replacement (32, 37, 54, 65, 95–98)	8	3	1980 to 1997	16 (6 to 42)	100 (15 to 213)	0.8 (0.3 to 3.4)	0.7 (0.0 to 1.4)
Total knee replacement (95)	1	1	1993 to 1994	25	200	0.2	0.1
Hip fracture repair (36, 95)	2	2	1990 to 1994	25 and 32	73 and 200	3.0 and 7.8	0.7‡‡
Open prostatectomy (99, 100)	2	2	1989 to 1995	25 and 38	54 and 141	0.2 and 0.5§	0.1 and 0.2§
Transurethral prostatectomy (54, 101)	2	2	1980 to 1991	9 and 10	22 and 101	0.9§ and 2.9§§	1.2§ and 0.5§§
Surgery for ruptured cerebral aneurysm (102, 103)	2	2	1984 to 1993	1 and 6	5 and 100	15.0 and 19.2	5.8 and 9.0
Surgery for unruptured cerebral aneurysm (103)	1	1	1987 to 1993	6	100	8.0	9.0

* For each study, we calculated (if possible) the absolute difference in mortality rate between the highest- and lowest-volume strata reported. All mortality rates reflect in-hospital death unless otherwise specified. Two reviewed studies of surgery for abdominal aortic aneurysm (52, 104) are not classified here because they analyzed ruptured and unruptured cases together. Values reported with "and" are values from individual studies rather than medians. NA = not available.

† Definitions indicate the thresholds below or above which a hospital was considered low or high volume.

‡ Volume was primarily analyzed as a continuous variable with no high- or low-volume threshold specified.

§ 30-day mortality rate.

‖ Farley and Ozminkowski (37) reported a 2.2% decrease in the in-hospital mortality rate per each 10% increase in volume.

¶ One study of primary coronary angioplasty for acute myocardial infarction (30) is not included here but is included in the overall findings.

** Negative numbers indicate that high-volume hospitals had higher mortality rates than low-volume hospitals.

†† Roohan and coworkers (25) published data for 5-year survival, not short-term mortality. Patients receiving care at the lowest-volume hospitals had a 60% higher risk for death within 5 years than those undergoing surgery at high-volume hospitals.

‡‡ Value given is for one study only. Data from the other study were not available.

§§ 60-day mortality rate.

Table 3. **Summary of Articles Examining Associations between Physician Volume and Death***

Procedure or Condition (Reference)	Studies Included	Studies with a Significant Volume–Outcome Association	Range of Time Periods Studied	Median Cases per Year Defining Low Volume (Range)†	Median Cases per Year Defining High Volume (Range)†	Median Average Mortality Rate (Range)	Median Absolute Difference in Mortality Rate for High vs. Low Volume (Range)
	n				*n*		%
AIDS (105)	1	1	1984 to 1994	1	35	NA	NA‡
Myocardial infarction (106)	1	1	1993	12	13	NA	NA§
Coronary angioplasty (29, 31, 47, 49, 107)	5	1	1990 to 1997	75 (25 to 85)	138 (50 to 250)	1.0 (0.7 to 2.5)	0.06 (−0.3 to 0.7)‖
Coronary artery bypass (33, 52, 111)	3	3	1986 to 1992	55 (51 to 116)	150 (116 to 259)	3.7 (2.4 to 4.4)	2.2 (0.8 to 5.7)
Pediatric cardiac surgery (57)	1	1	1992 to 1995	74	75	6.8	2.9
Carotid endarterectomy (23, 59, 60, 62–64, 66, 69, 70, 108, 109, 112)¶	12	7	1980 to 1995	8 (1 to 30)	30 (5 to 50)	2.0 (0.7 to 2.8)‡	1.4 (1.2 to 5.8)
Surgery for unruptured abdominal aortic aneurysm (73)	1	0	1985 to 1987	2	10	7.6	3.2
Surgery for ruptured abdominal aortic aneurysm (73, 77, 78)	3	3	1985 to 1997	4**	10**	53.6 (46.3 to 54.9)	14.5**
Pancreatic cancer surgery (85, 86)	2	1	1984 to 1995	1 and 9	10 and 42	8.0 and 12.9	7.0 and 10.2
Breast cancer surgery (22)	1	1	1980 to 1988	10	50	NA	NA††
Colorectal cancer surgery (52, 91–93, 110)	5	4	1983 to 1997	12 (5 to 21)	22 (9 to 40)	3.0 (2.0 to 6.0)	1.9 (1.4 to 1.9)
Lung cancer surgery (93)	1	0	1994 to 1997	22	132	1.9	1.1‡‡
Gastric cancer surgery (52, 93)	2	2	1986 to 1997	1 and 2	2 and 12	6.2 and 12.2	4.0 and 5.7
Total hip replacement (96–98)	3	2	1988 to 1992	9 (2 to 10)	27 (10 to 100)	0.4 (0.3 to 1.3)	0.0 and 1.7

* For each study, we calculated (if possible) the absolute difference in mortality rate between the highest- and lowest-volume strata reported. All mortality rates reflect in-hospital death unless otherwise specified. Values reported with "and" are values from individual studies rather than medians. NA = not available.

† Definitions indicate the thresholds below or above which a physician was considered low or high volume.

‡ Adjusted relative risk for death was 0.69 for patients of high-volume physicians compared with lowest-volume physicians.

§ Patients of high-volume physicians had lower in-hospital mortality rates (odds ratio, 0.89).

‖ Negative numbers indicate that high-volume physicians had higher mortality rates than low-volume physicians.

¶ 30-day mortality rate.

** Value given for one study only. Data from other studies were not available.

†† Patients with high-volume surgeons had better 5-year survival (odds ratio, 0.85).

‡‡ Difference in mortality rates between high- and low-volume surgeons was of borderline statistical significance ($P = 0.08$).

simultaneously. For some procedures, effects of only hospital or only physician volume seemed to be significant. Therefore, policies advocating selective referral to high-volume providers based solely on hospital (or physician) volume may not achieve their intended effect; a low-volume surgeon at a high-volume hospital may have significantly poorer results than a moderate-volume surgeon at a moderate-volume hospital (33). Other important synergistic relationships between effects of hospital and physician volume probably exist as well.

Even when a compelling volume–outcome relationship existed, our review revealed wide variations in the definitions of high and low volume for a given topic. This made it difficult to specify evidence-based recommendations about which institutions or physicians are truly high-volume providers suitable for "selective referral." For almost every condition or procedure for which at least three studies were identified, the thresholds used to define high and low volume overlapped substantially, that is, the definition of high volume in one study was the number used to indicate low volume in another. In many studies, the providers with the lowest volume (often ≤1 case per year) seemed to have markedly worse results than providers in the other volume categories, although formal statistical analysis of these comparisons was often lacking. More detailed research will be needed to determine the conditions or procedures for which a policy of "selective avoidance" of very-low-volume providers might be more appropriate than selective referral to high-volume (or very-high-volume) providers.

Most of the studies we reviewed examined the volume of services at one period in time; very few explored changes in volume and performance over time. This is important because complication rates and caseload numbers change over time. Over the past 20 years, mortality rates for almost all major procedures have decreased because of major advancements in surgical technique, anesthesia practice, and perioperative management (34, 35, 111). Conversely, the annual volume of some operations, such as carotid endarterectomy, has doubled in less than a decade, so that providers who were low volume through the early to mid-1990s may have much higher annual caseloads a few years later (35, 113). Because most of the studies we reviewed were based on data from the 1980s to mid-1990s, the extent to which their findings reflect current practice and volume is unclear.

The few studies that analyzed longitudinal trends in volume–outcome relationships found that the relative and absolute differences in performance between high- and low-volume providers narrowed over time (12, 34, 111). In addition, articles that tracked changes in individual hospital volume over time found that fluctuating numbers of cases within the same institution had no or minimal effects on outcomes (36, 37, 114). This suggests that volume–outcome relationships may reflect fixed differences in the overall quality between high- and low-volume providers, rather than the principle of "practice makes perfect."

Missing from most of the research we reviewed was an exploration of the mechanism through which volume influences outcomes. Volume is clearly a proxy measure of other things because it cannot directly produce good or bad results. Specific processes of care, correlated with volume, are the most likely explanatory factors. High-volume hospitals or physicians may use effective treatments more often than their low-volume counterparts. In one study of myocardial infarction, differential use of therapies proven to be effective (thrombolytics, aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and revascularization) explained one third of the survival advantage attributed to high-volume hospitals (21). Future investigations of volume–outcome relationships may be able to make important contributions by identifying specific differences in clinical management or procedural techniques between high-volume providers with good outcomes and low-volume provider with poor ones. Such studies would not only help uncover the mechanism through which caseload influences health but may also discover ways to achieve better outcomes in many procedures for which randomized, controlled trials are not feasible.

It is important to emphasize that any relationship between volume and outcome is true only on average. Outcomes vary widely among individual hospitals and physicians. Some low-volume providers have good outcomes, and some high-volume providers have poor outcomes. In New York State's 2000 report on cardiac surgery, almost half (47%) of high-volume CABG hospitals (≥500 procedures per year) and one third of high-volume cardiac surgeons (≥150 procedures per year) had risk-adjusted mortality rates that were greater than the statewide average (115).

Our study has some limitations. First, we cannot be sure that we identified all relevant studies because MEDLINE does not uniformly catalog this topic. However, we used a broad electronic search strategy, examined bibliographies by hand, and contacted experts in the field. Second, we cannot exclude a negative publication bias that might have diminished the number of studies failing to report the expected association. Third, the literature was too heterogeneous to permit formal quantitative meta-analysis. Nonetheless, we believe the medians and ranges of the volume–outcome effects we report will provide important and generalizable data by which to assess the magnitude and meaning of these relationships.

CONCLUSION

Twenty years of research have established that, for some procedures and conditions, higher volume among hospitals and physicians is associated with better outcomes. However, the magnitude of the relationship varies greatly among individual procedures and conditions. The clinical and policy significance of this finding is complicated by methodologic shortcomings of many studies. Even when a significant association exists, volume does not predict outcome well for individual hospitals or physicians. Investigating precisely what physicians and hospitals with high volumes and good outcomes do differently from those with low volume and poor outcomes is likely to contribute substantially to our knowledge and our ability to improve care for all patients.

APPENDIX: MEDLINE SEARCH ALGORITHM

Our search algorithm was as follows: AIDS[mesh] OR liver diseases/surgery[mesh] OR lung diseases/surgery[MESH] OR coronary artery bypass[mesh] OR endarterectomy,carotid[mesh] OR neoplasms/surgery[mesh]OR angioplasty[mesh] OR myocardial infarction[mesh] OR vascular surgical procedures[mesh]OR peripheral vascular diseases/surgery[mesh]OR arthroplasty,replacement,knee[mesh]OR arthroplasty,replacement,hip[mesh]) AND utilization[subheading] AND (volume[Text word] OR frequency[Text word] OR frequent [Text word] OR statistics[subheading]) AND (outcome assessment[mesh] OR outcome and process assessment[mesh] OR outcome[Text word] OR regionalization [text word]).

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The Choice: Lewellys F. Barker and the Full-Time Plan

Charles S. Bryan, MD, and M. Shawn Stinson, MD

In 1914, Lewellys F. Barker, William Osler's successor as Professor of Medicine and physician-in-chief at Johns Hopkins University School of Medicine, resigned to enter private practice rather than accept the terms of a full-time plan, whereby professors in clinical departments would be salaried like other professors in the university. Barker had been an early proponent of the full-time plan. His decision reflected not only a personal desire for a larger income but also contradictions inherent in the Flexnerian ideal of clinical medicine as a research-oriented university discipline devoid of financial incentives to see patients. In private practice, Barker maintained a high profile as a teacher, writer, supporter of the Johns Hopkins medical institutions, and public figure. The issues raised by his difficult decision remain relevant and have not been satisfactorily resolved.

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Commercialism in academic medicine, faculty compensation, and the relationship of full-time to part-time or volunteer faculty are delicate issues in American medicine that have never been satisfactorily resolved. These issues came to the forefront in 1914 when Lewellys F. Barker, William Osler's successor as Professor of Medicine at the Johns Hopkins University School of Medicine and physician-in-chief at the Johns Hopkins Hospital, resigned to enter private practice rather than accept the terms of a full-time plan, whereby professors in clinical departments would receive fixed salaries and have no financial incentives to see patients. Barker had been an early proponent of the full-time plan and never rejected its basic premise. He made significant contributions as a private practitioner, but the predicaments he faced in 1914 continue to pester the medical profession in the United States.

THE FULL-TIME PLAN

Until 1913, professors in clinical departments at medical schools in the United States typically earned most of their income in private practice. Osler, for example, would now be considered a part-time professor. He generally taught in the morning and then spent his afternoons in a practice that became quite lucrative but left him harried. Therefore, in 1905, he readily accepted the invitation to a more leisurely lifestyle at Oxford (1, 2). The full-time plan began on 23 October 1913 when the General Education Board of the Rockefeller Foundation resolved to fund full-time professorships at Johns Hopkins. The background story, familiar to medical historians, featured as dramatis personae the anatomist Franklin P. Mall, the pathologist William H. Welch, the educator Abraham Flexner, the industrialist John D. Rockefeller, and the Baptist minister Frederick T. Gates, who became Rockefeller's adviser in philanthropic matters (3, 4). Others included the pathologist Simon Flexner (Abraham Flexner's brother) and Osler. After reading *The Principles and Practice of Medicine* by Osler, Gates determined that funding scientific medicine would be the best use of Rockefeller funds. This led to the Rockefeller Institute for Medical Research, with Simon Flexner as director and Welch as president. Gates also concluded that scientific medicine would advance only if clinical departments were placed on the same basis as others within the university, meaning that professors would devote most of their time and energy to teaching and research. This idea resonated with a group of basic-science faculty at Johns Hopkins, where Welch and Mall had reached the same conclusion. After his 1910 report on the sorry state of most medical schools in the United States, Abraham Flexner embraced the idea and later joined the General Education Board, where he displaced Gates in power and influence and oversaw the creation of The William H. Welch Endowment for Clinical Education and Research. Barker, who was close to all of these men except Rockefeller and Abraham Flexner, was apparently the first physician to champion the full-time plan in public (5).

Lewellys Franklin Barker (1867 to 1943), like Osler, was a native of Ontario and the son of a minister. He came to Baltimore in 1891 at Osler's invitation and secured a residency position with Osler when another man canceled his plans. For most of the next 9 years, Barker lived in the Administration Building of the Johns Hopkins Hospital, where he worked first with Osler in medicine and then with Welch and Simon Flexner in pathology and Mall in anatomy. Although he apparently intended, from the onset, to make clinical medicine his career, Barker was steered by his mentors toward a thorough grounding in basic science. He became an authority on the histology of the nervous system and, at Mall's urging, studied extensively in Germany. Barker was especially impressed by Friedrich von Müller of Munich, the great clinician–teacher who stressed the importance of experimentation in clinical medicine. In 1899, on Mall's recommendation, Barker was appointed professor and chair of anatomy at the University of Chicago. President Daniel C. Gilman of Johns Hopkins called his departure "a real loss" (6).

Barker was close to Osler (**Figure 1**), but Mall (**Figure 2**) would be the more influential mentor. Between 1900 and March 1905, Mall wrote Barker at least 74 personal letters. Mall expressed his "deep satisfaction over your successes" (7) and reinforced "the advantage in having the medical work absolutely blended with the university—& this will tell in the long run" (8). Mall's opportunity to

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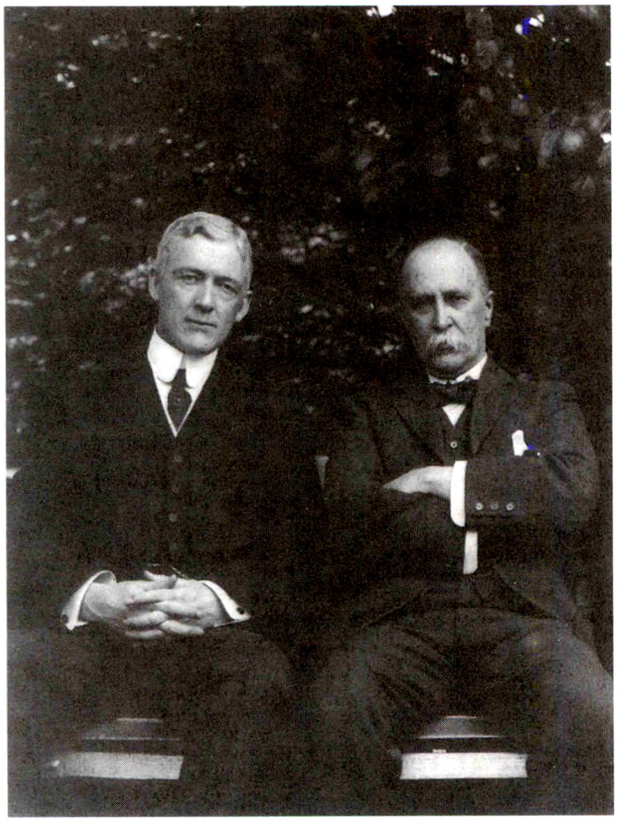
Figure 1. **Lewellys F. Barker (*left*) with William Osler in 1909.**



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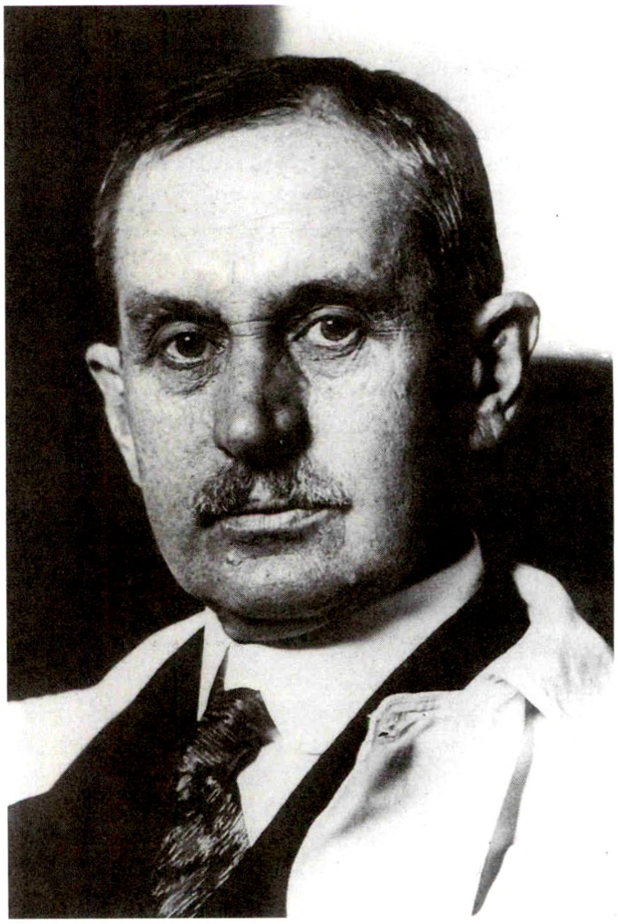
secure the eloquent Barker as his spokesperson came on 28 February 1902, when Barker was invited to address the Western Alumni of the Johns Hopkins University on the occasion of the university's 25th anniversary. Barker's topic was "Medicine and the Universities." Barker argued that if true university hospitals could be created through substantial endowments, "the men engaged to work in them should be chosen with the same care as to talents, attainments and personality as is exercised in the choice of any other professor in the university." Full-time clinical faculty members, he argued, should be well paid and should not engage in private practice. If and when they should ever see private patients in difficult cases, "the fees received from them might be contributed to the budgets of the hospitals themselves, in order to remove all temptation" (9). Welch applauded Barker's comments as being "undoubtedly on the right track" (10).

When Osler announced his intent to resign from the faculty in 1904, Mall led Barker's campaign for the professorship. He kept Barker informed about the search process, telling him that it was on the "clinical [side] that the opposition took its stand" but that a strong group wanted "a real professor who is willing to take the next step" (11). The choice came down to three of Osler's favorite protégés: Barker, William S. Thayer, and George Dock. Although he may have preferred Thayer, Osler chose not to force the issue and wrote Barker, "I am taking Plato's advice and sitting under a wall until the storm is over" (12). When the decision was made in Barker's favor, the elated Mall outlined a detailed "Program for Life" for Barker (13).

The fly in the ointment was that the money was not available for an adequate full-time salary. Mall told Barker that the arrangements would be "Dr. Osler's salary & a little practice at the hospital" (14). Barker confided to his wife, "Dr. Mall thinks that I should make no conditions but say plain yes or no" (15). Osler departed Baltimore on 15 May 1905 to be succeeded by Barker at a modest salary that could be supplemented through private practice.

At first, Barker met Mall's expectations. Within his department, he developed a biological laboratory, a biochemical laboratory, and a physiological laboratory. These laboratories, which were prototypes for today's research-oriented divisions within departments of medicine, made

Figure 2. **Franklin Paine Mall, principal architect of the full-time plan.**



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experimental clinical research a priority at Johns Hopkins (16, 17). To a large extent, Barker gradually expelled the reservations that some had expressed about his clinical abilities and, as Osler had done, established a private practice at his residence. Meanwhile, Welch actively championed the full-time plan (18). He gained the support of successive Hopkins deans (19), pursued the idea with Gates, and developed a written proposal that led in 1911 to a formal request to John D. Rockefeller for $1.2 million to Johns Hopkins "for the establishment of full time" (20). For reasons that have never been entirely clear, the monies were not appropriated until 1913, although opposition from Osler and others may have been a factor. Welch recognized that "at least in the inception of the plan the men who would be desired and would be fitted for the chief positions could accept them only at a large pecuniary sacrifice" (21). Under Welch's proposal, professors would be salaried at $10 000, associate professors at about $2500, and chiefs of the clinical laboratory at $1500. A $10 000 salary in 1914 would be $178 700 in year 2002 dollars (based on Consumer Price Index, U.S. Bureau of Labor Statistics), which is well below the 20th percentile for chairs of departments of medicine in the United States (22). On 14 February 1914, a formal memorandum of agreement was reached between the General Education Board and the Johns Hopkins University, whereby the Departments of Medicine, Surgery, and Pediatrics would be put on a full-time basis. William S. Halsted, the chair of surgery, and John Howland, the chair of pediatrics, accepted, but Barker declined. Welch asked Barker if he would accept a $20 000 salary if it could be arranged. Barker, who would later write that Welch "was almost as naive about personal finances as the average debutante" (23), replied cordially but coolly that because the suggestion was hypothetical, he would not comment on it (24). Barker was gracious at meetings (25), smiled at a cartoon in the *Baltimore American* implying that physicians at Johns Hopkins had been made mercenary by the lures of private practice, and offered to help his successor, Theodore C. Janeway of New York. Barker spent the remaining 29 years of his life in private practice in Baltimore.

THE CHOICE

Why did Barker reject for himself the full-time plan that he had helped create? At least three reasons can be advanced, of which the most obvious was the desire for a larger income. His family of origin had been poor, he had learned to be entrepreneurial early in life, he had paid for his own education with outside jobs, he had married and grown accustomed to a good lifestyle, and he had incurred a financial burden as a result of his first child's acquired mental retardation caused by meningoencephalitis. A second explanation can be derived from Barker's personal trajectory, as understood from today's perspectives on career development and the adult life cycle (26). By 1914, Barker had "become his own man," and Mall was no longer a significant mentor. His major organizational impact on the Department of Medicine at Johns Hopkins lay behind him, he had no personal research agenda, and he had become interested in patient care. The final possible reason for Barker's rejection of the full-time plan is that he probably realized, at least subconsciously, contradictions inherent in the Flexnerian ideal of clinical medicine as a research-oriented university discipline devoid of incentives for practice. This ideal was, in fact, controversial on both sides of the Atlantic (27–29), and even Germany's von Müller attacked the full-time system as "directly prejudicial to the teacher and to the school" (28). There is no evidence that Barker embraced the attitude, sometimes bordering on hostility, that Mall and certain other basic scientists of that era held toward clinical faculty who earned income through patient care (30).

Osler, among others, thought that Barker had been treated unfairly. He wrote Barker, "It seems to me too that there is an ethical question in this,—how far the Trustees or the Faculty have the right to change conditions under which you accepted the professorship" (31). He later added, "You have been harshly treated from the standpoint of ordinary academic courtesy" (32). However, Barker never spoke against the full-time plan, despite encouragements to do so, and never offended the plan's protagonists. He held fast to the belief that the full-time plan encouraged experimental medicine (33). Barker remained close to Welch whom he served as personal physician. Gates, who also saw Barker as a patient (34), praised him privately: "To your ideals . . . we owe I suppose more than to any other factor our present progress" (35). Barker would later urge "utilization of both whole-time men and part-time men in clinical work" for its "many advantages over an exclusively whole-time or an exclusively part-time staff" (36).

Barker thrived in private practice but continued to contribute to academic medicine. He organized an efficient model of group practice that allowed him to devote substantial time, including lengthy summer vacations, to intellectual pursuits. At Johns Hopkins, he continued his popular weekly clinics; served on numerous committees; succeeded Welch in 1926 as chairman of the Medical Board; and influenced a wealthy patient, Lucy James, who gave Johns Hopkins $400 000 that enabled the building of a Woman's Clinic. He urged cooperation among specialties, espoused what is now called the ***biopsychosocial model of disease***, delineated the relationship of generalist physicians to consultants, outlined a comprehensive approach to diagnosis, promoted teaching in nonuniversity hospitals, and underscored the coming importance of genetics and geriatrics. He held major visiting professorships. He served as vice-president of the American Medical Association and as president of the Association of American Physicians, the Association for the Study of Internal Secretions, and the Southern Medical Association. He became a sought-after speaker and a public figure, giving popular advice to the laity about how to deal with the stresses of everyday life; how to eat properly; how to succeed (37); and how to *Live Long and Be Happy*, the title of one of his books (38). On 7 March 1934, Barker represented the medical profession at a symposium in Madison Square Garden on "The Case of Civilization versus Hitlerism." After 1914, Barker wrote almost 200 papers, 12 books, and an autobiography. He died in 1943, leaving an estate valued at $219 818, or $2.3 million in year 2002 dollars.

CONCLUSIONS

In "The Choice," William Butler Yeats observed: "The intellect of man is forced to choose/Perfection of the life or of the work." Barker's choice afforded him a great deal of both. As Osler's successor at Johns Hopkins, he had helped to usher in a new era of clinical science based on experimentation. In practice, he exemplified the ability of private physicians to contribute substantially to medical education and to the public welfare. In retrospect, the full-time plan, as conceived by Mall, Welch, and others and as articulated in Barker's seminal address on "Medicine and the Universities," was flawed by ambiguities inherent in the relationships between and among universities, medical schools, hospitals, and physicians in private practice. The full-time plan for clinical faculty—that is, the strict full-time plan as opposed to the "geographic" full-time plan, whereby faculty could supplement their incomes through practice—did not succeed (39, 40). However, the growth of clinical faculties during the 20th century markedly reduced the role of private practitioners in medical education (41, 42). Moreover, the "active invasion of the hospitals by the universities," proposed by Osler (43) and others, did not anticipate the problematic expansion of universities into numerous areas of service-oriented economic relevance (44). Barker eventually concluded: "The private practice of medicine works well in America" (45). Ideally, adequate public funding of medical education would render the dependence of medical schools on practice income unnecessary; full-time faculty would be rewarded mainly for excellence in teaching, research, and scholarship; and individuals could shift back and forth between full-time faculties and the private sector as their priorities change within a seamless medical profession. However, and in summary, the dilemma faced by Barker in 1914 reflects tensions that seem largely insolvable at present, at least within the context of a free and pluralistic society.

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Screening for Osteoporosis in Postmenopausal Women: Recommendations and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendations on screening for osteoporosis and the supporting scientific evidence and updates the 1996 USPSTF recommendations on this topic. The complete USPSTF recommendation and rationale statement on this topic, which includes a brief review of the supporting evidence, is available through the USPSTF Web site (www.preventiveservices.ahrq.gov), the National Guideline Clearinghouse (www.guideline.gov), and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (telephone, 800-358-9295; e-mail, ahrqpubs@ahrq.gov). The complete information on which this statement is based, including evidence tables and references, is available in the accompanying article in this issue and in the summary of the evidence and the systematic evidence review on the Web sites already mentioned.

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See related article on pp 529-541.

*For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

SUMMARY OF RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends that women 65 years of age and older be screened routinely for osteoporosis. The USPSTF recommends that routine screening begin at 60 years of age for women at increased risk for osteoporotic fractures (see Clinical Considerations for a discussion of women at increased risk). This is a **grade B recommendation.** (See **Appendix** Table 1 for a description of the USPSTF classification of recommendations.)

The USPSTF found good evidence that the risk for osteoporosis and fracture increases with age and other factors, that bone density measurements accurately predict the risk for fractures in the short term, and that treating asymptomatic women with osteoporosis reduces their risk for fracture. (See **Appendix** Table 2 for a description of the USPSTF classification of levels of evidence.) *The USPSTF concludes that the benefits of screening and treatment are of at least moderate magnitude for women at increased risk by virtue of age or presence of other risk factors.*

The USPSTF makes no recommendation for or against routine osteoporosis screening in postmenopausal women who are younger than 60 years of age or in women 60 to 64 years of age who are not at increased risk for osteoporotic fractures. This is a **grade C recommendation.**

The USPSTF found fair evidence that screening women at lower risk for osteoporosis or fracture can identify additional women who may be eligible for treatment for osteoporosis, but it would prevent a small number of fractures. The USPSTF concludes that the balance of benefits and harms of screening and treatment is too close to make a general recommendation for this age group.

CLINICAL CONSIDERATIONS

Modeling analysis suggests that the absolute benefits of screening for osteoporosis among women 60 to 64 years of age who are at increased risk for osteoporosis and fracture are comparable to those of routine screening in older women. The exact risk factors that should trigger screening in this age group are difficult to specify based on evidence. Lower body weight (weight < 70 kg) is the single best predictor of low bone mineral density (1, 2). Low weight and no current use of estrogen therapy are incorporated with age into the three-item Osteoporosis Risk Assessment Instrument (1). There is less evidence to support the use of other individual risk factors (for example, smoking, weight loss, family history, decreased physical activity, alcohol or caffeine use, or low calcium and vitamin D intake) as a basis for identifying high-risk women younger than 65 years of age. At any given age, African-American women on average have higher bone mineral density than white women and are thus less likely to benefit from screening.

Among different bone measurement tests performed at various anatomic sites, bone density measured at the femoral neck by dual-energy x-ray absorptiometry is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Other technologies for measuring peripheral sites include quantitative ultrasonography, radiographic absorptiometry, single-energy x-ray absorptiometry, peripheral dual-energy x-ray absorptiometry, and peripheral quantitative computed tomography. Recent data suggest that peripheral bone density testing in the primary care setting can also identify postmenopausal women who have a higher risk for fracture over the short term (1 year). Further research is needed to determine the accuracy of peripheral bone density testing in comparison with dual-energy x-ray absorptiometry. The likelihood of being diagnosed with osteoporosis varies greatly depending on the site and type of bone measurement test, the number of sites tested, the brand of densitometer used, and the relevance of the reference range.

Estimates of the benefits of detecting and treating osteoporosis are based largely on studies of bisphosphonates. Some women, however, may prefer other treatment options (for example, hormone replacement therapy, selective estrogen receptor modulators, or calcitonin) based on personal preferences or risk factors. Clinicians should review with patients the relative benefits and harms of available treatment options, and uncertainties about their efficacy and safety, to facilitate an informed choice. No studies have evaluated the optimal intervals for repeated screening. Because of limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in bone mineral density; however, longer intervals may be adequate for repeated screening to identify new cases of osteoporosis. Yield of repeated screening will be higher in older women, those with lower bone mineral density at baseline, and those with other risk factors for fracture.

There are no data to determine the appropriate age to stop screening and few data on osteoporosis treatment in women older than 85 years of age. Patients who receive a diagnosis of osteoporosis fall outside the context of screening but may require additional testing for diagnostic purposes or to monitor response to treatment.

The brief review of the evidence and other sections that are normally included in USPSTF recommendations are available in the complete recommendation and rationale statement on the USPSTF Web site (www.preventiveservices.ahrq.gov).

RECOMMENDATIONS OF OTHERS

In 1998, the National Osteoporosis Foundation, in collaboration with other professional organizations, issued screening guidelines recommending bone density testing for all women 65 years of age or older, as well as younger postmenopausal women who have had a fracture or who have one or more risk factors for osteoporosis (3). Collaborating groups included the American Academy of Orthopaedic Surgeons, the American College of Obstetricians and Gynecologists, the American Geriatrics Society, the American College of Radiology, the American College of Rheumatology, the American Academy of Physical Medicine and Rehabilitation, the American Association of Clinical Endocrinologists, the Endocrine Society, and the American Society for Bone and Mineral Research. The American Association of Clinical Endocrinologists released revised guidelines in 2001 (4). A 2000 Consensus Development Conference sponsored by the U.S. National Institutes of Health concluded that the value of universal osteoporosis screening was not yet established (5). The conference panel recommended an individualized approach to screening, noting that bone density measurement is appropriate when it will aid the patient's decision to institute treatment. The Canadian Task Force on Preventive Health Care is currently revising its recommendations on screening for osteoporosis.

APPENDIX

Members of the U.S. Preventive Services Task Force are Alfred O. Berg, MD, MPH, *Chair* (University of Washington, Seattle, Washington); Janet D. Allan, PhD, RN, CS, *Vice-Chair* (School of Nursing, University of Maryland, Baltimore, Baltimore, Maryland); Paul S. Frame, MD (Tri-County Family Medicine, Cohocton, and University of Rochester, Rochester, New York); Charles J. Homer, MD, MPH (National Initiative for Children's Healthcare Quality, Boston, Massachusetts); Mark S. Johnson, MD, MPH (University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey); Jonathan D. Klein, MD, MPH (University of Rochester School of Medicine, Rochester, New York); Tracy A. Lieu, MD, MPH (Harvard Pilgrim Health Care and Harvard Medical School, Boston, Massachusetts); Cynthia D. Mulrow, MD, MSc (University of Texas Health Science Center, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Texas); C. Tracy Orleans, PhD (The Robert Wood Johnson Foundation, Princeton, New Jersey); Jeffrey F. Peipert, MD, MPH (Women and Infants' Hospital, Providence, Rhode Island); Nola J. Pender, PhD, RN (University of Michigan, Ann Arbor, Michigan); Albert L. Siu, MD, MSPH (Mount Sinai School of Medicine, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Co., Inc., West Point, Pennsylvania); Carolyn Westhoff, MD, MSc (Columbia University College of Physicians and Surgeons, New York, New York); and Steven H. Woolf, MD, MPH (Virginia Commonwealth University, Fairfax, Virginia).

Appendix Table 1. **U.S. Preventive Services Task Force Grades and Recommendations***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

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CLINICAL GUIDELINES

Screening for Postmenopausal Osteoporosis: A Review of the Evidence for the U.S. Preventive Services Task Force

Heidi D. Nelson, MD, MPH; Mark Helfand, MD, MPH; Steven H. Woolf, MD, MPH; and Janet D. Allan, PhD, RN

Background: **Although osteoporotic fractures present an enormous health burden, it is not clear whether screening to identify high-risk persons is appropriate.**

Purpose: **To examine evidence on the benefits and harms of screening postmenopausal women for osteoporosis.**

Data Sources: **MEDLINE (1966 to May 2001), HealthSTAR (1975 to May 2001), and Cochrane databases; reference lists; and experts.**

Study Selection: **English-language abstracts that included original data about postmenopausal women and osteoporosis and addressed the effectiveness of risk factor assessment, bone density tests, or treatment were included.**

Data Extraction: **Selected information about patient population, interventions, clinical end points, and study design were extracted, and a set of criteria was applied to evaluate study quality.**

Data Synthesis: **No trials of the effectiveness of screening have been published. Instruments developed to assess clinical risk factors for low bone density or fractures have moderate to high sensitivity and low specificity. Among different bone density tests measured at various sites, bone density measured at the femoral neck by dual-energy x-ray absorptiometry is the best predictor of hip fracture. Women with low bone density have approximately a 40% to 50% reduction in fracture risk when treated with bisphosphonates.**

Conclusions: **Population screening would be based on evidence that the risk for osteoporosis and fractures increases with age, that the short-term risk for fracture can be estimated by bone density tests and risk factors, and that fracture risk can be reduced with treatment. The role of risk factor assessment and different bone density techniques, frequency of screening, and identification of subgroups for which screening is most effective remain unclear.**

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See related article on pp 526-528.

Half of all postmenopausal women will have an osteoporosis-related fracture during their lives, including one quarter who will develop a vertebral deformity (1) and 15% who will suffer a hip fracture (2). Hip fractures are associated with high mortality rates and loss of independence (3, 4). Although many vertebral fractures are detected only incidentally on radiography, some cause severe pain, leading to 150 000 hospital admissions per year in persons older than 65 years of age, 161 000 physician office visits, and more than 5 million days of restricted activity in those 45 years of age or older (5).

Low bone density has been used to predict risk for fractures as well as to diagnose osteoporosis. Osteoporosis has been defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (6, 7). This definition emphasizes that, in addition to bone mass, the structure of bone is an important factor in the pathogenesis of fractures.

A World Health Organization working group (8) proposed that osteoporosis should be diagnosed in epidemiologic studies when bone mineral density is 2.5 SDs or more below the mean for healthy young adult women at the spine, hip, or wrist (corresponding to a T-score ≤ -2.5) or when patients have a history of atraumatic fracture (9). By the World Health Organization definition, up to 70% of women older than 80 years of age have osteoporosis (10). Age is also an important factor in the relationship between bone density and the absolute risk for fracture. Older women have a much higher fracture rate than younger women with the same bone density because of increasing risk from other factors, such as bone quality and tendency to fall (11).

Despite the high prevalence of osteoporosis and the effect of fractures on mortality, independence, and quality of life, it is not clear whether it is appropriate to screen asymptomatic postmenopausal women. Recent systematic reviews and guidelines disagree about which women should be screened and when (12–20). This disagreement reflects, in part, gaps in the evidence. For example, most guidelines recommend using risk factors to select patients for bone density testing, but because of inadequate data there is no consensus on which risk factors to use. As part of the U.S. Preventive Services Task Force update of its 1996 recommendation (21), we examined evidence on the benefits and harms of screening postmenopausal women for osteoporosis. Specifically, we addressed the role of risk factors in identifying high-risk women, techniques of bone density testing to identify fracture risks, effectiveness of treatment in reducing fracture risk, and harms of screening and treatment.

METHODS

Additional methods used for this review, including determination of the quality of studies (22), are detailed in **Appendix Tables 1, 2, and 3** (available at www.annals.org) and in a separate report (23). The analytic framework and key questions are detailed in the **Appendix Figure** (available at www.annals.org). Relevant studies were identified from multiple searches of MEDLINE (1966 to May

2001), HealthSTAR (1975 to May 2001), and Cochrane databases; reference lists of systematic reviews; and experts. We also sent letters to manufacturers of bone density devices requesting additional information about the performance of their instruments, but we received no new data.

Two reviewers read each abstract to determine its eligibility. We included English-language abstracts that contained original data about postmenopausal women and osteoporosis and addressed screening or the effectiveness of risk factor assessment, bone density testing, or treatment. We considered screening to be the process of assessing postmenopausal women without known osteoporosis for risk of osteoporotic fractures by identification of risk factors, including low bone density. Postmenopausal women were those who had experienced surgical or natural menopause, regardless of age. Women with preexisting atraumatic fractures were not considered in the screening population because they had confirmed osteoporosis according to the World Health Organization definition.

For studies of prediction, we selected articles that reported the relationship between risk factor assessment methods or bone density tests and bone density, bone loss, or fractures. We reviewed studies of medications used for treatment and present results for bisphosphonates. We focused on randomized, controlled trials of therapies reporting radiographically verified, nontraumatic fracture outcomes because fractures are a stronger measure of effectiveness than bone density. We excluded studies of primary prevention of osteoporosis, such as the role of nutrition, calcium consumption, and physical activity. We also excluded secondary causes of osteoporosis, such as corticosteroid use and certain chronic diseases, and studies that did not provide sufficient information to allow determination of the method for selecting patients and for analyzing data. Investigators read the full-text versions of the retrieved papers and reapplied the initial eligibility criteria. To assess the internal validity of individual studies, we applied a set of criteria developed by the third U.S. Preventive Services Task Force (**Appendix Table 1**, available at www.annals.org) (22).

In this paper, we highlight studies that are applicable to current practice standards, have high-quality internal validity ratings, and are most generalizable to the U.S. population of postmenopausal women under consideration for screening. We created an outcomes table to summarize the number of hip and vertebral fractures prevented based on age-specific prevalence rates and treatment effects obtained from results of the reviewed studies. We conducted a sensitivity analysis to determine the influence of risk factors on the number needed to screen.

This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the U.S. Preventive Services Task Force. Agency staff and Task Force members participated in the initial design of the study and reviewed interim analyses and the final manuscript. Additional reports were distributed for review to content experts and revised accordingly before preparation of this manuscript (23, 24). The authors are responsible for the content of the manuscript and the decision to submit it for publication.

RESULTS

Studies of Screening

We identified no studies about the effectiveness of screening in reducing osteoporotic fractures. Without direct evidence from screening studies, recommendations about screening need to rely on evidence that risk factor assessment or bone density testing can adequately identify women who could ultimately benefit from treatment.

Risk Factor Assessment

Hundreds of studies report associations between risk factors and low bone density and fractures in postmenopausal women (24). The most comprehensive study of risk factors in a U.S. population is the Study of Osteoporotic Fractures, a good-quality prospective study of 9516 women 65 years of age and older (25). In this study, 14 clinical risk factors were identified as significant predictors of hip fracture in multivariable models (age; maternal hip fracture; no weight gain; height; poor self-rated health; hyperthyroidism; current use of benzodiazepines, anticonvulsants, or caffeine; not walking for exercise; lack of ambulation; inability to rise from a chair; poor scores on two measures of vision; high resting pulse; and any fracture since 50 years of age). The relative risk for hip fracture per decrease of 1 SD in calcaneal bone density was 1.6 (95% CI, 1.3 to 1.9). This was comparable to the magnitude of the relative risks of most of the other significant predictors in the model, which ranged from 1.2 to 2.0. Women with at least 5 of the 14 risk factors had increased rates of hip fractures compared with those who had 0 to 2 risk factors at all levels of calcaneal bone density.

To determine which risk factors could be important in women younger than 65 years of age, we reviewed eight observational studies of risk factors and fractures of various types conducted in populations in which at least 50% of participants were younger than 65 years of age. **Table 1** lists risk factors that were statistically significant predictors for fractures in multivariable models (26–33). These results could not be quantitatively combined because risk factors were defined differently in each study.

Results of risk factor studies have been used to assess risk in individuals. We identified 10 cross-sectional studies that described methods of determining risk for low bone density for individual women based on selected clinical risk factors (**Table 2**) (34–43). The most common methodologic limitations of these studies are lack of validation and lack of generalizability because of small numbers of patients or nonrepresentative patients. We also identified 8 studies of clinical risk factors to determine fracture risk (**Table 2**) (44–51). None of these studies received a good rating for internal validity. Four studies evaluated hip frac-

Table 1. **Risk Factors for Fractures in Women 50–65 Years of Age**

Risk Factor	Relative Risk for Fracture (95% CI)	Reference
Age		
Per 2 y	1.11 (1.01–1.21)	26
Per 5 y	1.94 (1.55–2.42)	27
Body mass index		
Per increase of 10 kg/m^2	0.58 (0.36–0.92)	27
$\geq$25.6 kg/m^2	wrist, 0.7 (0.5–0.9); ankle, 1.6 (1.0–2.4)	26
$\geq$28.6 kg/m^2	wrist, 0.5 (0.4–0.7); ankle, 2.0 (1.3–3.1)	26
Low	1.1 (1.0–1.2)	29
Height (per 0.1 m)	1.58 (1.18–2.12)	27
Mother with fracture	1.27 (1.16–1.40)	30
Grandmother with hip fracture	3.70 (1.55–8.85)	31
Hormone replacement therapy		
Current use	0.82 (0.74–0.91)	30
Per 5 y of use	0.5 (0.2–0.9)	28
>2 y of use	0.44 (0.22–0.89)	32
Long history of use	0.70 (0.50–0.96)	33
African American ethnicity	0.54 (0.41–0.72)	30
Diabetes mellitus	9.17 (3.38–24.92)	27
Chronic conditions	1.3 (1.1–1.5)	26
Disability pension	3.79 (2.15–6.68)	27
Long-term work disability	1.3 (1.1–1.6)	26
Self-rated health (fair or poor)	1.79 (1.52–2.11)	30
Moderate daily physical activity	0.61 (0.37–0.99)	32
Alcohol		
$\geq$100 g/wk	1.70 (1.08–2.67)	33
Regular use	1.4 (1.3–4.4)	29
1 to 6 drinks/wk	0.85 (0.75–0.96)	30
Smoking		
Current	1.5 (1.3–1.5); 1.14 (1.00–1.30)	26, 30
Former	1.09 (1.00–1.19)	30
$\geq$11 cigarettes/d	3.0 (1.9–4.6)	26
Unmarried	2.16 (1.28–3.64)	27
College education or higher	1.26 (1.16–1.38)	30
Age at menopause	0.94 (0.88–0.99)	32
Time since menopause		30
10–19 y	1.18 (1.01–1.38)	
20–29 y	1.31 (1.12–1.54)	
30 y	1.51 (1.26–1.81)	
Oophorectomy before age 45	3.64 (1.01–13.04)	33
$\geq$5 children	2.5 (1.1–6.7)	29

ture outcomes, two evaluated vertebral fractures, and two evaluated all types of fractures. These studies described the association of risk factors with fractures known to have occurred already (four case–control studies) or how well they would predict fractures in the future (four prospective cohort studies).

A recent study compared the performance of five clinical decision rules for bone density testing among 2365 postmenopausal women 45 years of age or older who were enrolled in a community-based study of osteoporosis in Canada (52). These rules included guidelines from the National Osteoporosis Foundation (53); the Simple Calculated Osteoporosis Risk Estimation (SCORE) rule (age, weight, ethnicity, estrogen use, presence of rheumatoid arthritis, history of fractures) (41); the Osteoporosis Risk Assessment Instrument (ORAI) (age, weight, current use of hormone replacement therapy) (43); the Age, Body Size, No Estrogen rule (54); and body weight criterion (weight < 70 kg) (38). None of the decision rules had good discriminant performance. In this study, SCORE and ORAI had the highest area under the receiver-operating characteristic curves (0.80 and 0.79, respectively [sensitivity, 99.6% and 97.5%; specificity, 17.9% and 27.8%, respectively]). Details of how to use SCORE and ORAI are given in Table 2.

Bone Density Tests

Several technologies are available to measure bone density (55–58), although correlations among different bone density devices are low (0.35 to 0.60) (59–79). Dual-energy x-ray absorptiometry is considered the gold standard because it is the most extensively validated test against fracture outcomes. When used in the same patients, dual-energy x-ray absorptiometry machines from different manufacturers differ in the proportion of patients diagnosed as having osteoporosis by 6% to 15% (80–85). Published studies consistently show that the probability of receiving a diagnosis of osteoporosis depends on the choice of test and site (86–90). One analytic study, for example, found that 6% of women older than 60 years of age would receive a diagnosis of osteoporosis if dual-energy x-ray absorptiometry of the total hip were used as the only test, compared

Table 2. **Studies of Risk Factor Assessment***

Study, Year (Reference)	Design	Participants, *n*	Validated	Risk Factors Included	Outcome
Bone density outcomes					
Slemenda et al., 1990 (34)	Cross-sectional	124	No	Age, height, weight, calcium intake, caffeine intake, alcohol and tobacco use, urinary markers of bone turnover	Correct classification of high or low BMD (lowest third of participants)
Falch et al., 1992 (35)	Cross-sectional	73	Yes	Low body weight, reduced renal phosphate reabsorption, smoking	Bone loss
Ribot et al., 1992 (36)	Cross-sectional	1565	No	Weight, menopause, duration of menopause	Vertebral BMD < −2 SD
Elliot et al., 1993 (37)	Cross-sectional	320	Yes	Spine BMD: age, weight, smoking status, age at menarche; femoral neck BMD: age, weight, family history, activity, smoking status	Low lumbar spine and femoral neck BMD (lowest third of age-matched normal range)
Michaëlsson et al., 1996 (38)	Cross-sectional	175	No	Weight > 70 kg	Femoral neck BMD < −2.5 SD
Verhaar et al., 1998 (39)	Cross-sectional	61	No	Arm span–height difference of ≥3 cm; arm span–height difference, age < or > 70 y, and whether arm span was < or >160 cm	BMD ≤−2.5 SD and vertebral fracture
Ballard et al., 1998 (40)	Cross-sectional	1158	No	Age, age at menopause, height, weight, gravidity, parity, current use of steroids, current use of HRT	Osteoporosis of femoral neck, spine, or both
Lydick et al., 1998 (41)	Cross-sectional	1279	Yes	SCORE = age (3 × first digit of age in years), weight (−1 × weight in pounds/10 and truncated to integer), ethnicity (5 if not black), estrogen use (1 if never used), rheumatoid arthritis (4 if present), history of fractures (4 for each fracture after age 45 y of wrist, hip, or rib, to a maximum of 12)	Femoral neck BMD ≤−2 SD
Goemaere et al., 1999 (42)	Cross-sectional	300	No	18-item questionnaire of risk factors for osteoporosis (ethnicity; height loss; age; weight; smoking, coffee, alcohol, dairy product use; activity; family history; existence of comorbid conditions; history of wrist fracture; menopause before age 45 y; corticosteroid use)	Lumbar spine, femoral neck, and hip BMD
Cadarette et al., 2000 (43)	Cross-sectional	926	Yes	ORAI = age (15 points if ≥75 y, 9 if 65–74 y, 5 if 55–64 y), weight (9 if <60 kg, 3 if 60–69.9 kg), current use of HRT (2 if not currently using)	Hip or lumbar spine BMD ≤−2.5 SD
Fracture outcomes					
Kleerekoper et al., 1989 (44)	Case–control	663	No	Model 1: total months of lactation, family history of osteoporosis, years postmenopause, weight Model 2: breastfed, surgical menopause, age at menarche, age, smoking status	Vertebral fractures
van Hemert et al., 1990 (45)	Cohort	1014	No	Age, metacarpal cortical area, relative cortical area, BMI, height, diameter of forearm, diameter of knee, age at menarche, age at menopause, smoking, number of children, period of lactation	Osteoporotic fractures
Cooper et al., 1991 (46)	Case–control	1012	No	Age, height, vertebral fracture after age 45 y, age at last menstrual period, number of children, ever use of oral corticosteroids	Vertebral fractures
Wolinsky and Fitzgerald, 1994 (47)	Cohort	368	No	White ethnicity, female sex, living in southern United States, age, hospitalization in the previous year, previous fall, body mass	Hip fractures
Johnell et al., 1995 (48)	Case–control	5618	No	Late menarche, poor mental score, low BMI, low level of physical activity, little exposure to sunlight, and low consumption of calcium and tea	Hip fractures
Ranstam et al., 1996 (49)	Case–control	7474	No	Mental–functional risk score: knowledge of the day of week, knowledge of age, ability to wash, ability to dress	Hip fractures
Tromp et al., 1998 (50)	Cohort	1469	No	Female sex, living alone, past fractures, inactivity, height, use of analgesics	Probability of fractures
Burger et al., 1999 (51)	Cohort	5208	No	Model with BMD: age, sex, height, use of a walking aid, current smoking, BMD of femoral neck Model without BMD: age, sex, height, use of a walking aid, current smoking, weight	Hip fractures

* BMD = bone mineral density; BMI = body mass index; HRT = hormone replacement therapy; NPV = negative predictive value; PPV = positive predictive value; ORAI = Osteoporosis Risk Assessment Instrument; ROC = receiver-operating characteristic (≥0.80 usually indicates effectiveness); SCORE = Simple Calculated Osteoporosis Risk Estimation.

† Based on criteria developed by the U.S. Preventive Services Task Force (22).

with 14% with dual-energy x-ray absorptiometry of the lumbar spine, 3% with quantitative ultrasonography, and 50% with quantitative computed tomography (87).

The likelihood of receiving a diagnosis of osteoporosis also depends on the number of sites tested. Testing in the forearm, hip, spine, or heel generally identifies different

Table 2—**Continued**

Performance	Quality Rating†
Midshaft radius: 68% low, 77% high Lumbar spine: 61% low, 45% high Femoral neck: 66% low, 53% high	Poor
Sensitivity, 36%; specificity, 89%; PPV, 74%	Poor
Sensitivity, 73%; specificity, 66%	Fair
Lumbar spine: sensitivity, 86%; specificity, 32% Femoral neck: sensitivity, 89%; specificity, 25%	Fair
Sensitivity, 94%; specificity, 36%; PPV, 21%; NPV, 97%	Fair
Arm span only: sensitivity, 58%; specificity, 56% Arm span, age, arm span length: sensitivity, 81%; specificity, 64%	Poor
ROC area, 0.73	Fair
Sensitivity, 89%; specificity, 50%; ROC area, 0.81 using a score of ≥6	Good
Lumbar spine: ROC area, 0.66 Femoral neck: ROC area, 0.69 Hip: ROC area, 0.76	Fair
Sensitivity, 95%; specificity, 41%, using a score of ≥9	Good
Model 1: mean ROC area ± SE, 0.55 ± 0.07; sensitivity, 56%; specificity, 54% Model 2: mean ROC area ± SE, 0.51 ± 0.042; sensitivity, 63% specificity, 39%	Fair
Sensitivity, 48%; specificity, 82%	Fair
Sensitivity, 51%; specificity, 69%	Fair
ROC area, 0.71; sensitivity, 64.7%; specificity, 65.7%	Fair
Sensitivity, 55%; specificity, 65%	Fair
A less than perfect score had a sensitivity of 46% and a specificity of 79%	Fair
No predictors, 0%; 4 predictors, 12.9%	Fair
Model with BMD: ROC area, 0.88; sensitivity, 70%; specificity, 84% Model without BMD: ROC area, 0.83; sensitivity, 70%; specificity, 83%	Fair

groups of patients. For example, a physician cannot definitively say that a patient does not have osteoporosis on the basis of a forearm test alone. Conversely, although test results at any site are associated to some degree with fractures at other sites, a physician may not be able to assess whether a patient with a low T-score on a hand or forearm test has substantial bone loss at other sites.

A meta-analysis assessed 23 publications from 11 separate prospective cohort studies published before 1996 (91). Nearly all of the data were from women in their late 60s or older. No studies of ultrasonography were included. The meta-analysis indicated that dual-energy x-ray absorptiometry at the femoral neck predicted hip fracture better than measurements at other sites and was comparable to forearm measurements for predicting fractures at other sites (92–94). For bone density measurements at the femoral neck, the pooled relative risk per decrease of 1 SD in bone density was 2.6 (CI, 2.0 to 3.5). In direct comparisons, heel ultrasonography was slightly worse than but comparable to dual-energy x-ray absorptiometry of the hip in women older than 65 years of age (**Table 3**) (92, 94–100). For both tests, a result in the osteoporotic range is associated with an increased short-term probability of hip fracture. No data compare dual-energy x-ray absorptiometry and ultrasonography for prediction of fracture in women younger than 65 years of age.

The National Osteoporosis Risk Assessment study (30) recently evaluated the performance of peripheral densitometry in predicting fractures. This prospective study of ambulatory postmenopausal women 50 years of age or older with no previous osteoporosis diagnoses recruited 200 160 participants from 4236 primary care practices in 34 U.S. states. Women received baseline T-scores by measuring bone density at the heel (single-energy x-ray absorptiometry or quantitative ultrasonography), forearm (peripheral dual-energy x-ray absorptiometry), or finger (peripheral dual-energy x-ray absorptiometry). After 12 months of follow-up, women with T-scores less than or equal to −2.5 had an adjusted risk for all types of fractures that was 2.74 (CI, 2.40 to 3.13) times higher than women with normal baseline bone density. Results varied by type of test and site; those identified as osteoporotic by dual-energy x-ray absorptiometry had higher fracture rates. Tests were not compared with dual-energy x-ray absorptiometry of the femoral neck, and the study did not describe how tests performed by age group or risk category.

Treatment

The U.S. Food and Drug Administration has approved hormone replacement therapy, bisphosphonates, raloxifene, and calcitonin for osteoporosis prevention or treatment, or both. Our review of estrogen and selective estrogen receptor modulators is presented elsewhere (101).

A recent meta-analysis (102) of 11 randomized trials (103–113) enrolling 12 855 women found that at least 5 mg of alendronate per day reduced vertebral fractures in 8 trials (relative risk, 0.52 [CI, 0.43 to 0.65]). Alendronate also reduced forearm fractures in 6 trials involving 3723 participants (dosage, ≥10 mg/d; weighted relative risk,

Table 3. **Prospective Studies of Dual-Energy X-Ray Absorptiometry and Ultrasonography That Reported Hip Fractures***

Cohort (Reference)	Sample	Age (Range)	Follow-up	Participants	Probability of Hip Fracture†				
						DEXA of the Hip		QUS of the Heel	
						Low Risk	High Risk	Low Risk	High Risk
			y	*n*					
Study of Osteoporotic Fractures (92, 94–96)	Community-dwelling white women from 4 areas in the United States who were recruited from lists	≥65	1.8–2.9	5236	0.009	0.005	0.023	0.006	0.018
		65–79	2.9					0.006	0.23
		≥80	2.9						
		65–69	1.8	2371	0.003	0.0028	0.005		
		70–74	1.8	3013	0.0076	0.005	0.016		
		75–79	1.8	1728	0.007	0.003	0.019		
		80–84	1.8	731	0.018	0.007	0.049		
		≥85	1.8	291	0.024	0.014	0.028		
Epidemiologie de L'Osteoporose (97–100)	Women from 5 cities in France who were recruited from voting lists and health insurance companies	≥75	2	5656	0.02	0.033	0.008	0.012	0.029
		<80	2	3982	0.013	0.002	0.025		
		≥80	2	3616	0.028	0.006	0.04		

* DEXA = dual-energy x-ray absorptiometry; QUS = quantitative ultrasonography.
† Probability of hip fracture if bone density was classified as high or low risk.

0.48 [CI, 0.29 to 0.78]), hip fractures in 11 trials involving 11 808 participants (dosage, ≥5 mg/d; weighted relative risk, 0.63 [CI, 0.43 to 0.92]), and other nonvertebral fractures in 6 trials involving 3723 participants (dosage, 10 to 40 mg/d; weighted relative risk, 0.51 [CI, 0.38 to 0.69]). These trials included follow-up data ranging from 1 to 4 years; effect sizes for longer periods of use are not known. We evaluated data from these trials to determine whether women who have a similar overall risk for fracture but different bone densities derive similar benefit from treatment. This question is clinically important because accepted criteria for initiating treatment are lacking.

The Fracture Intervention Trial (FIT) of alendronate was conducted with two groups of participants and provides some information about levels of risk. One group (FIT-I) included a higher-risk sample of 2027 women who had T-scores of −1.6 or lower and preexisting vertebral fractures (104). The 3-year risk for hip fracture was 2.2% in the placebo group and 1.1% in the alendronate group (relative hazard, 0.49 [CI, 0.23 to 0.99]), and the 3-year risk for any clinical fracture was 18.2% in the placebo group and 13.6% in the alendronate group (relative hazard, 0.72 [CI, 0.58 to 0.90]). A second study from FIT (FIT-II) included a lower-risk sample of 4432 women who also had T-scores of −1.6 or lower but did not have preexisting vertebral fractures (114). The 4-year incidences of hip fracture (1.1%) and any clinical fractures (14.1%) in the placebo group were lower than those observed in the FIT-1 placebo group. In FIT-II, only the subgroup of treated patients who had T-scores lower than −2.5 (n = 1627) had a significant risk reduction for all clinical fractures, from 19.6% to 13.1% (relative risk, 0.64 [CI, 0.50 to 0.82]). No reduction in risk for fractures was seen in patients who had T-scores between −1.6 and −2.5.

The results from FIT suggest that women with more risk factors for fracture relating to bone structure and integrity, such as age, very low bone density, or preexisting vertebral fractures, derive the greatest absolute benefit from treatment. However, FIT did not examine other nonskeletal risk factors, such as psychomotor impairment, poor gait, and other factors that increase the risk for falling. The effect of some of these risk factors on the benefit of treatment was examined in a randomized trial of another bisphosphonate, risedronate (115). Risedronate had no effect on hip fracture rates among women 80 years of age or older who had one or more risk factors for falls but who did not necessarily have low bone density. In the same report, in women 70 to 79 years of age with severe osteoporosis (T-score < −3), risedronate reduced hip fractures by 40% (relative risk, 0.6 [CI, 0.4 to 0.9]; number needed to treat for benefit, 77).

Trial results are not applicable to a screening program unless the trials included patients who would be identified by screening the general population. We examined recruitment and eligibility characteristics of the 10 published randomized trials of alendronate to assess whether selection biases or other biases might have affected their generalizability (**Table** 4) (103–112). Overall, the trials included relatively healthy women with low bone density who were not using estrogen. Except for participants in two trials involving women who had recently gone through menopause and were not osteoporotic, most participants were older than 65 years of age.

The FIT-II is the largest study and provided the most detailed description of recruitment and results (107). In FIT-II, researchers recruited the sample of 4432 women by mailing a query to more than 1 million women selected from the general population in 11 cities. Women who had medical problems (for example, dyspepsia) or who used estrogen were excluded. Fifty-four thousand women (approximately 5.4%) responded by telephone; of these, 26 137 (52%) had a screening visit. A higher than expected proportion of these (65%) had sufficiently low bone density to enroll in the study. Of this 65%, 57% were classified as "ineligible, did not wish to continue, or screened after recruitment to this arm." It is not clear from this description how many patients did not meet the eligibility criteria. In addition, an unspecified number of patients (up to 28 000) were found to be ineligible at the initial stage of recruitment. The demographic characteristics of eligible and screened but excluded participants were not reported. None of the other randomized trials disclosed any details of how their samples were recruited or how many respondents were found to be ineligible before randomization.

In other clinical areas, the results of industry-sponsored trials were significantly more favorable to newer therapies than trials funded by nonprofit organizations (116, 117). Because all 11 trials of alendronate were funded wholly or in part by the manufacturer, we were unable to assess the influence of sponsorship on effect size. If effectiveness of treatments is less than estimated in these trials, the efficiency of screening to identify candidates for treatment will be reduced and the number needed to screen for benefit will increase.

Harms

Several potential harms are associated with screening and treatment. A test result indicating osteoporosis could produce anxiety and perceived vulnerability (118) that may be unwarranted. On a quality-of-life questionnaire, women with osteoporosis voiced significantly more fears than women who had normal bone density (119). Some women may be falsely reassured if abnormal results from last year's dual-energy x-ray absorptiometry of the hip appear "improved" on this year's normal calcaneal ultrasonogram. The potential time, effort, expense, and radiation exposure of repeated scans over a lifetime have not yet been determined.

Potential harms may also arise from inaccuracies and misinterpretations of bone density tests. The variation among techniques, along with the lack of methods to integrate bone density results with clinical predictors, makes it difficult for clinicians to provide accurate information to patients about test results. In one study, physicians found densitometry reports confusing and were not confident that their interpretations of T-scores were accurate (120). False-positive results could lead to inappropriate treatment, and false-negative results could lead to missed treatment opportunities.

Harms of treatment depend on the medication used. Overall, gastrointestinal side effects occur in approximately 25% of patients taking alendronate, but in controlled trials these rates were usually not significantly higher than those for placebo. High rates of serious gastrointestinal side effects have been observed among Medicare enrollees taking

Table 4. **Randomized, Controlled Trials of Alendronate with Fracture Outcomes***

Study, Year (Reference)	Duration	Age	Sample	Exclusion Criteria†	Participants Lost to Follow-up	Quality Rating‡
	y				*n/n (%)*	
Adami et al., 1995 (103)	2	48–76	9 Italian centers; T-score < −2 (0.67 g/cm^2); 5% vertebral fractures	Narrow	32/211 (15.2)	Fair to good
Black et al., 1996 (104)	3	55–81	11 U.S. cities; BMD <0.68 g/cm^2; no previous vertebral fractures	Broad (medical illness, dyspepsia)	81/2027 (4)	Good
Bone et al., 1997 (105)	2	>60	15 U.S. sites; BMD <0.84 g/cm^2; average of 20 y since menopause; 30.7% vertebral fractures	Broad (medical illness, NSAIDs, GI drugs)	19/359 (5.3)	Fair to good
Chesnut et al., 1995 (106)	2	42–75 (avg. 63)	7 centers; spine BMD <0.88 g/cm^2; average hip BMD, 0.7 g/cm^2; ≥5 y since menopause	Broad	26/157 (16.6)	Fair
Cummings et al., 1998 (107)	4	55–81	11 U.S. cities; BMD <0.68 g/cm^2 (average, 0.59 g/cm^2); no previous vertebral fractures	Broad (medical illness, dyspepsia)	179/4432 (4)	Good
Greenspan et al., 1998 (108)	2.5	>65	1 Boston center; no BMD entry criteria	Narrow ("good health")	33/120 (27.5)	Fair
Hosking et al., 1998 (109)	4	45–59	4 centers; BMD >0.8 g/cm^2; <10% prevalent vertebral fractures	Narrow ("good health")	287/1499 (19.1)	Fair
Liberman et al., 1995 (110)	3	45–80	2 multicenter trials; T-score <−2.5; 21% prevalent vertebral fractures	Narrow ("good health")	170/994 (17.1)	Good
McClung et al., 1998 (111)	3	40–59	15 centers; T-score <−2; 6–36 mo since menopause; no previous vertebral fractures	Narrow ("good health," estrogen use)	(31 at 3 y)	Fair
Pols et al., 1999 (112)	1	40–82 (mean 63)	153 centers; T-score <−2.8	Narrow ("good health")	211/1908 (11.1)	Fair

* BMD = bone mineral density; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.
† In general, "narrow" criteria excluded estrogen users and patients with illnesses affecting bone metabolism.
‡ Based on criteria developed by the U.S. Preventive Services Task Force (22).

Table 5. **Screening for Osteoporosis in 10 000 Postmenopausal Women: Hip and Vertebral Fracture Outcomes by 5-Year Age Intervals***

Variable	Age Group					
	50–54 y	**55–59 y**	**60–64 y**	**65–69 y**	**70–74 y**	**75–79 y**
Base-case assumptions†						
Prevalence of osteoporosis	0.0305	0.0445	0.065	0.120	0.2025	0.285
Relative risk for hip fracture with treatment	0.63	0.63	0.63	0.63	0.63	0.63
Relative risk for vertebral fracture with treatment	0.52	0.52	0.52	0.52	0.52	0.52
Adherence to treatment	0.7	0.7	0.7	0.7	0.7	0.7
Results, *n*						
Identified as high risk (osteoporotic)	305	445	650	1200	2025	2850
Hip fractures prevented	1	2	5	14	39	70
NNS to prevent 1 hip fracture	7446	4338	1856	731	254	143
NNT to prevent 1 hip fracture	227	193	121	88	51	41
Vertebral fractures prevented	5	7	22	40	95	134
NNS to prevent 1 vertebral fracture	1952	1338	458	248	105	75
NNT to prevent 1 vertebral fracture	60	60	30	30	21	21

* NNS = number needed to screen for benefit; NNT = number needed to treat.

† Estimates for assumptions include age-specific prevalence rates for osteoporosis and probabilities of fractures; relative risk of 0.63 for hip fractures and 0.52 for vertebral fractures with treatment; treatment adherence of 0.7 (see text). Formulas for calculations are described in Appendix Table 2.

alendronate (121). The long-term adverse effects of alendronate are unknown.

Costs of screening vary with technique, and average 2000 Medicare reimbursement rates were $133 for dual-energy x-ray absorptiometry and $34 for ultrasonography (122). Abnormal results on ultrasonography may require confirmatory dual-energy x-ray absorptiometry before treatment because clinical trials are based on entry criteria using dual-energy x-ray absorptiometry. Most women would require repeated tests over several years before receiving a diagnosis of osteoporosis and leaving the screening pool. Treatment costs also vary; alendronate currently costs approximately $3 per daily dose.

Screening Strategies

To estimate the effect of screening 10 000 postmenopausal women for osteoporosis on reducing hip and vertebral fractures, we created an outcomes table based on assumptions from the reviewed studies (**Table 5**). These estimates include age-specific prevalence rates expressed in 5-year age intervals (123) and treatment effects based on trial results (risk reduction, 37% for hip fracture and 50% for vertebral fracture) (102, 104, 115, 124). We estimated an adherence rate of 70% based on reports of adherence and side effects from treatment trials, assuming less optimal adherence in the general population.

When the assumptions in **Table 5** are used, if 10 000 women 65 to 69 years of age underwent bone densitometry (dual-energy x-ray absorptiometry of the femoral neck), 1200 would be identified as high risk (T-score ≤ -2.5). If these women were offered treatment that resulted in a 37% reduction in hip fracture risk and a 50% reduction in vertebral fracture risk and 70% adhered to therapy, then 14 hip fractures and 40 vertebral fractures would be prevented over a 5-year period. The number of women in this age group needed to screen to prevent one hip fracture in 5 years would be 731, and the number of women with low bone density needed to treat for benefit would be 88. The number needed to screen to prevent one vertebral fracture would be 248, and the number needed to treat for benefit would be 30. Treatment has significant costs and potential harms; when the number needed to screen for benefit is high, the balance of benefits and harms may become unfavorable. These numbers become more favorable in older persons because the prevalence of osteoporosis increases steadily with age.

There is interest in whether risk assessment can be used to select patients for bone densitometry, which is costly. Our literature review indicated that the prevalence of osteoporosis, the predictability of densitometry, and the effectiveness of treatment might be lower for younger than for older postmenopausal women. To determine whether it is useful to consider clinical risk factors when screening younger postmenopausal women, we also included risk estimates for clinical risk factors in a sensitivity analysis. Our review of observational studies with younger postmenopausal women indicated that three consistent predictors of fracture are increasing age, low weight or body mass index, and nonuse of hormone replacement therapy (defined by current use, ever use, or certain durations of use). These three variables are also used in ORAI to identify women with low bone density (43) and were the variables most strongly associated with low bone density in a study enrolling mostly younger postmenopausal women in the United States (125). On the basis of these studies, we estimated that one of these risk factors increases the probability of having osteoporosis by up to 100% and increases the risk for fracture by 70% (relative risk, 1.7).

For younger age groups, the presence of clinical risk factors influences outcomes. For example, only five hip fractures are prevented over 5 years when all women 60 to 64 years of age are screened; however, nine hip fractures are prevented if women have a factor that increases fracture risk by 70%. For women 60 to 64 years of age who have such a risk factor, the number needed to screen is 1092 and the number needed to treat for benefit is 72 to prevent 1 hip fracture. These numbers approach those of women 65 to 69 years of age (**Figure**).

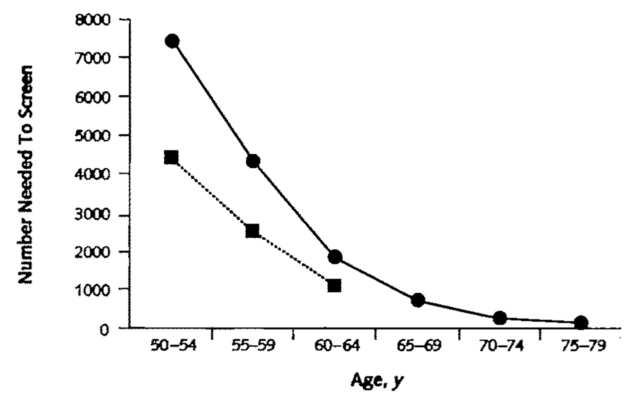
DISCUSSION

Although many studies have been published about osteoporosis in postmenopausal women, no trials have evaluated the effectiveness of screening; therefore, no direct evidence that screening improves outcomes is available. Instruments developed to assess clinical risk factors for low bone density or fractures generally have moderate to high sensitivity and low specificity. Many have not been validated, and none have been widely tested in a practice setting. Among different bone density tests measured at various sites, bone density measured by dual-energy x-ray absorptiometry at the femoral neck is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Heel ultrasonography and other peripheral bone density tests, however, can also predict short-term fracture risk. Bisphosphonates decrease fracture risk by approximately 40% to 50% in women with low bone density.

Support for population screening would be based on evidence that the prevalences of osteoporosis and fractures increase with age, that the short-term risk for fracture can be estimated by bone density tests and risk factors, and that the fracture risk among women with low bone density can be significantly reduced with treatment. We applied these data to generate an outcomes table of screening strategies that provides estimates of the numbers of women needed to screen and treat to prevent fractures. Age-based screening is supported by prevalence data, that is, the number needed to screen to prevent fractures decreases sharply as age and prevalence increase. Use of risk factors, particularly increasing age, low weight, and nonuse of estrogen replacement, to screen younger women may identify additional high-risk women and provide absolute benefit similar to that yielded by screening older women without risk factors. These findings relate to screening asymptomatic women only and do not apply to women considered for testing because of preexisting or new fractures or the presence of secondary causes of osteoporosis.

Our approach has several limitations, however, and results from a well-designed trial of screening strategies should supersede our estimations, which are based on indirect evidence. The estimates in the outcomes table are limited by assumptions that are arguable or highly variable by patient and setting. Our assumptions of treatment effect and adherence are especially optimistic and reflect results of clinical trials, not clinical practice. We chose a 5-year time horizon based on the short-term predictability of bone density tests as well as on results of short-term treatment trials. Long-term outcomes may provide a more accurate estimate of benefits. Also, we cannot exclude the possibility that harms outweigh benefits, particularly since the long-term effects of bisphosphonates are not yet known.

Figure. **Number needed to screen to prevent one hip fracture in 5 years.**



The dotted line indicates women with at least one risk factor; the solid line indicates women without risk factors.

The evidence on which we based our conclusions is also limited. Overall, evidence is stronger for women older than 65 years of age than for younger women because more research has been done in older age groups. Bone loss in the perimenopausal and early postmenopausal years is important to long-term bone health, but few published studies address screening and treatment for younger postmenopausal women. Fracture risk is determined not only by bone density but also by bone characteristics that are difficult to measure in a clinical setting, such as bone structure and morphologic characteristics. No bone density studies or treatment trials include large numbers of nonwhite women, and it may be difficult to provide ethnicity-specific screening recommendations in the absence of more evidence.

The role of clinical risk factors is still unclear. Although many risk factors are associated with osteoporosis and fractures, how to use them to select women to test or treat is uncertain. The risk factors identified by our literature review and used in the outcomes table are only best estimates. Other risk factors may prove to be equally predictive when used for screening purposes. Further validation of existing risk assessment instruments or development of new ones would be useful. Few studies have evaluated the effect of altering modifiable risk factors, such as smoking cessation, strength and balance training, and visual correction. These interventions may prove to be as effective as drug therapy in preventing fractures and may also be important effect modifiers that would alter the effectiveness of treatments.

Peripheral bone density tests have not been extensively studied for screening. Results from the National Osteoporosis Risk Assessment Study (30) indicate that peripheral tests can predict short-term fracture rates in a primary care population that would be targeted for screening. Most treatment trials use dual-energy x-ray absorptiometry of the hip as an entry criterion, and results may not apply to women whose diagnosis is determined by other tests. A sequential approach, in which women with low values on a peripheral test are subsequently tested by dual-energy x-ray absorptiometry of the hip to determine treatment needs, may be useful, although this approach has not been evaluated. Further research is needed to define the appropriate use of these technologies.

How frequently to screen has also not been specifically studied, but data are needed to determine optimal screening intervals. Estimations can be made based on the age-specific prevalence of osteoporosis and the precision of bone density tests. Less frequent testing for younger postmenopausal women when prevalence is lower (for example, 5-year intervals) and more frequent testing for older women (for example, 2-year intervals) might be reasonable, but further research is needed. Screening intervals of less than 2 years seem unwarranted because the precision error of densitometry would likely exceed the estimated bone loss in such a brief period (126). After a woman is screened and determined to have osteoporosis, future screening with bone density testing would be unnecessary.

Osteoporotic fractures present an enormous health burden on an expanding elderly population. Further research to more accurately determine the benefits and harms of screening is of paramount importance.

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Specialist Evaluation in Chronic Kidney Disease: Too Little, Too Late

Maintenance of patients with end-stage renal disease (ESRD) on long-term dialysis is a triumph of modern medicine. In the United States alone, more than 250 000 persons with ESRD, who otherwise would have died, enjoy life—usually of good quality—because of the availability of hemodialysis and peritoneal dialysis. Yet this triumph has a tragic flaw: The lifespan of dialysis patients remains abnormally short. Only about one third survive 5 years. Even patients who start dialysis in their 40s have no more than a 50% chance to live 5 more years (1).

Nephrologists caring for patients receiving long-term dialysis have studied and improved several factors that contribute to this high mortality, including some technical features of dialysis and various clinical aspects of the care of patients with ESRD. Nevertheless, mortality rates have remained disappointingly high. One area that has received increasing attention over the past decade is the timeliness of referral of persons with chronic renal failure to nephrologists (2, 3). A consensus statement from the National Institutes of Health recommends that patients should be referred as soon as plasma creatinine levels increase to 132 to 177 μmol/L (1.5 to 2.0 mg/dL) (4). There is some evidence that such early intervention by nephrologists may improve morbidity and even mortality of persons receiving long-term dialysis, but it is by no means conclusive (2, 3).

In this issue, Kinchen and colleagues (5) provide important new information about the timing of referral of patients with chronic renal failure to nephrologists and the influence of this factor on survival once patients receive dialysis. The investigators prospectively studied more than 800 patients in 81 dialysis units in the United States. They found that nephrologists saw only about half of the patients at least 1 year before the initiation of dialysis. Thirty percent were seen less than 4 months before dialysis began—an interval that is clearly too short for the specialist to provide optimal intervention. For example, patients referred to nephrologists that late were less likely to have received erythropoietin before the start of dialysis or to have had timely placement of permanent vascular access. Most important, patients with diabetic kidney disease referred to nephrologists a year or more before the start of dialysis lived substantially longer than those referred within 4 months of beginning dialysis.

The relatively large number of patients and dialysis units and the prospective nature of the study strengthen the observation that late referral affects mortality. However, the study cannot be considered conclusive because no data were available regarding the time of initiation of dialysis in the course of progressive renal failure. As the authors note, it is possible that patients who received early referral to nephrologists started dialysis earlier in the course of disease than did patients who received late referrals. This would cause lead-time bias—that is, an apparent increase in longevity resulting from starting dialysis when renal failure was less advanced. Moreover, the correlation of survival with early referral to nephrologists does not prove a causal relationship. Timely referral may be only one aspect of superior primary care. To interpret the data of Kinchen and coworkers (5) and others (2, 3), we need information about the overall medical care of patients with chronic renal failure. Did they have primary care physicians? How regularly did they see these doctors? Were the physicians well informed about the management of persons with chronic renal failure?

What accounts for the late referral of patients to nephrologists? Kinchen and colleagues (5) identify African-American men, persons without medical insurance, and those with more comorbid conditions as especially likely to be referred belatedly. Older age and lack of higher education also correlate with late referrals. These observations suggest that broader issues about medical care may underlie late referral. The special peril of the African American, the uninsured, and the less well educated suggests that limited access to good primary care may be a critical factor for which delay in referral to specialists is only a marker. Persons with chronic renal failure may not be referred to specialists early enough because their generalist care is belated, erratic, discontinuous, or nonexistent. The erroneous presumption of some primary care physicians that elderly persons or those with comorbid conditions cannot be treated successfully with long-term dialysis may lead to delayed referral or even nonreferral, as may ethically dubious attitudes about the use of expensive technology for the elderly or other groups.

As important as the potential benefit of early referral in reducing mortality of patients receiving long-term dialysis is the possibility that good medical care of persons with early chronic renal failure may delay or even eliminate the need for dialysis. Compelling evidence supports the conclusion that in patients with early chronic renal failure, blockade of the renin–angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers slows deterioration of renal function, especially in patients with diabetic kidney disease (6, 7). Strict control of hypertension, management of hyperlipidemia, treatment of anemia with erythropoietin, and meticulous management of diabetes and its complications (8) are also important aspects of the care of persons with progressive renal failure. Most patients receiving dialysis die of cardiovascular disease, which clearly begins long before initiation of dialysis and deserves aggressive prophylactic treatment as soon as chronic renal failure is recognized.

All these forms of therapy are well within the skills of primary care physicians. It makes sense for generalists caring for persons with chronic renal failure to obtain early and periodic advice from a nephrologist and, in the care of diabetic patients, a diabetologist. Primary care doctors will benefit from up-to-date advice about the management of early renal failure. Specialists will be able to educate patients about alternative methods of dialysis and to facilitate timely placement of vascular access, an important factor in avoiding morbidity and needless hospitalizations for access problems. Such a coordinated approach not only should reduce the morbidity and mortality of persons who eventually require dialysis but, best of all, may delay or even eliminate the need for it in some fortunate patients.

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A Lesson in Poverty

Today I started working in the hospital located in the center of a bustling metropolis. As I walked toward the endoscopy suite, I could feel my confidence build. I had been well trained and I was ready. But after training in the United States for 7 years, the decision to come back to India was not an easy one. Most of my Indian friends who had gone to the States for advanced training had opted to stay. I had always wanted to return to India. Almost everyone advised me against leaving the States. Nor was it easy to convince my wife. But through my training I had honed my endoscopy skills to a fine degree and felt I could get access to the most difficult bile duct, could snare the most mischievous polyp, could be successful where many might have failed. And I had always felt that my country needed me. With my advanced training, I could return to help my people. I knew I would make a lot less money, but that had never been my priority. Being able to help my country was my primary goal. Getting a position in India to achieve that goal proved difficult. In the end my American connections helped with this as well.

In preparation for my return, I did my homework: brushed up on *Harrison's* tropical disease chapter, reacquainted myself with malaria and amoebic liver abscess, and made a mental note to put tuberculosis back to the top of the list of my differential diagnoses for almost all patients.

And so today I met my first patient: a young woman who recently had an attack of gallstone-induced pancreatitis and had been referred for endoscopic retrograde cholangiopancreatography to extract a nagging common bile duct stone. Her husband and three young children, the youngest less than a year old, accompanied her. I tried to explain the procedure in detail to the patient and her husband, stressing the long list of possible complications that might occur. Her husband quickly cut me short with an endorsement all too common in my country: "Doctor, you are like our God and if anything goes wrong in your hands that is our destiny."

I began the sedation wondering if my colleagues in Cleveland would have considered this to be informed consent.

But the procedure went smoothly. I performed a sphincterotomy and removed a few small common bile duct stones. The nurses transferred the patient to the recovery room.

I walked out of the endoscopy suite, found the patient's husband, and told him that everything had gone well. He was visibly relieved and told me that he had been confident his wife would be fine. He had heard that I had been trained in "phoren."

As I walked towards the hospital cafeteria for a cup of coffee the man quickly caught up to me again, attempting to strike up a conversation. He and his wife had come from the neighboring province, he said, about half a day's travel from the city. He was very poor; the couple worked as manual laborers in a road construction project. After his wife got sick he had borrowed 10 000 rupees (US $225) to come to the city for the best possible treatment. He had almost exhausted that money and was glad that that he would be able to return home soon with his family. He himself had been diagnosed recently with pulmonary tuberculosis but could not afford to continue the costly therapy for more than 2 months. He asked me if it was okay to do so. I struggled for an appropriate answer. He sensed my uneasiness, and I hastened to change the topic, saying that his wife would soon be on her way to recovery. He reflected that it would be nice to give her a chance to rest for few days, but she would have to go back to her dawn-to-dusk backbreaking work immediately. The loan sharks would make their lives miserable.

I glanced at the three children trotting behind us, the oldest boy half-carrying, half-dragging his baby sister. They were malnourished and potbellied, with unkempt hair, runny noses, and tattered clothes, eyeing the well-stocked hospital cafeteria hungrily. Undoubtedly they probably had not had anything to eat since morning, and it was now noon. I decided to give their father a 100-rupee note (US $2) to buy them some food, and walked away as fast as I could. The man mumbled his thanks and apologetically added, "Don't worry, Doctor, we will be fine; the Almighty takes care of us, the poor."

As I walked back to the endoscopy suit, my soul plummeted. I had forgotten this poverty of my country. Perhaps I never before saw it in this way. Had my western training somehow opened my eyes? At any rate, I felt ill equipped to handle it. There had not been, in my American training program, any sessions on coping with abject poverty.

Nevertheless, at some level I remain happy, secure in my decision to return. I have more to learn here. Learn it I will. And there will be no shortage of teachers.

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LETTERS

COMMENTS AND RESPONSES

Long-Term Outcome in Lupus Nephritis

TO THE EDITOR: Illei and colleagues (1) report superior long-term outcomes in patients with lupus nephritis treated with pulse cyclophosphamide with or without pulse methylprednisolone compared with those treated with pulse methylprednisolone alone. Their data also suggest that pulse methylprednisolone combined with cyclophosphamide has additional benefit. The primary outcomes defining treatment failure were need for supplemental immunosuppressive therapy, doubling of serum creatinine concentration, or death.

Illei and colleagues' mortality data, however, are intriguing. The investigators previously reported that after 5 years of follow-up, 3 of 55 cyclophosphamide-treated patients had died compared with 0 of 27 patients randomly assigned to pulse methylprednisolone alone (2). The suggestion of a true difference in mortality rates at a median of 11 years of follow-up is even more striking. In an intention-to-treat analysis combining Illei and colleagues' data on all cyclophosphamide-treated patients, we found that 10 of 55 (18%) cyclophosphamide-treated patients died versus only 1 of 27 patients (4%) treated with pulse methylprednisolone alone. This corresponds to a very large relative risk reduction of 78% in patients not exposed to cyclophosphamide. Although the authors report no significant difference among the treatment groups for the outcome of death, this difference has a *P* value of 0.09 using the conservative Fisher exact test. If the groups were compared by using a survival analysis (as was done for the composite end point used by the authors to define treatment efficacy), the *P* value would probably have been much closer to 0.05. With such small sample sizes, even *P* values between 0.05 and 0.10 should be addressed, particularly with regard to an outcome as important as death. Of interest, when an intention-to-treat analysis was used, no difference was seen in renal morbidity as an individual outcome between pulse methylprednisolone alone and cyclophosphamide-containing regimens. Only by using a composite end point that included the need for additional immunosuppressive therapy were the authors able to find an advantage to the cyclophosphamide-containing regimens. As the authors point out, a substantial percentage of patients in the methylprednisolone group ultimately received cyclophosphamide therapy. Perhaps on some level this composite analysis reflects the need for additional immunosuppressive therapy in many of the patients treated with methylprednisolone alone.

Mortality data should be a major consideration in the selection of therapy in patients with lupus nephritis. In patients with less severe disease, initial treatment with pulse methylprednisolone alone may be preferable, although salvage therapy with immunosuppressive agents may ultimately be necessary.

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IN RESPONSE: We agree with Spiera and colleagues that the larger number of deaths in the cyclophosphamide-containing groups in our study is intriguing and that a survival analysis is the optimal statistical method to determine whether there is a true difference in mortality. However, we believe that combining the mortality data from both cyclophosphamide-containing groups and comparing them with the methylprednisolone group is flawed because this method assumes that any increased mortality in the combination group is attributable to cyclophosphamide. Comparing the methylprednisolone-only group with the cyclophosphamide-only group in a Breslow–Gehan–Wilcoxon survival analysis showed no significant difference in risk for death. We agree that borderline *P* values should be interpreted cautiously with such a small number of patients because small differences from the expected number of events (a few more or less) may cause large changes in the *P* value. To distinguish chance statistical oddities from biologically plausible trends, these results should be analyzed in the context of previous experience. To determine whether there was a biologically plausible connection to cyclophosphamide treatment, we analyzed the individual causes of deaths. Only one of five deaths in the cyclophosphamide group could reasonably be attributed to immunosuppression (*Pneumocystis carinii* pneumonia). One patient died of a clearly unrelated cause: bleeding after a kidney biopsy at another center. Removing this patient from the survival analysis changed the *P* value to 0.13. We have not seen an increased risk for death in patients treated with cyclophosphamide in previous studies, either at the end of the study or during long-term follow-up (1, 2). Spiera and colleagues also point out that in an intention-to-treat analysis, the rate of end-stage renal disease did not differ among the groups. As discussed in our paper, this apparent equality can be explained by the design of the original study and the practice at our institution to use cyclophosphamide in patients in whom pulse methylprednisolone has failed.

Our major finding was that the addition of methylprednisolone pulses to pulse cyclophosphamide leads to better long-term responses in moderate to severe lupus nephritis without conferring additional risk for adverse events. Dr. Spiera and colleagues conclude that pulse methylprednisolone alone should be the preferable option to treat mild lupus nephritis. However, this is not an appropriate extrapolation from our study because neither the original protocol nor the follow-up was designed to address this question.

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Quality Indicators for Management and Prevention of Falls

TO THE EDITOR: I read with interest Rubenstein and colleagues' review on fall assessment and prevention (1). I was surprised that the authors did not comment on the fact that balance exercises, such as tai chi, were one of the best ways to reduce risk for falls. Also, although many trials showed a reduction in risk for falls, very few showed a reduction in risk for injurious falls. I think we should be concerned with fall prevention at an earlier age, when participation in such things as tai chi or yoga can be really helpful.

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Reference

1. Rubenstein LZ, Powers CM, MacLean CH. Quality indicators for the management and prevention of falls and mobility problems in vulnerable elders. Ann Intern Med. 2001;135(8 Pt 2):686-93. [PMID: 11601951]

IN RESPONSE: Exercise is one of the most potent interventions for both fall prevention and improvement of mobility dysfunction. Dr. Pierre is concerned that we omitted discussion of tai chi as being one of the best types of exercises for these purposes. We agree that tai chi is a beneficial form of exercise and discussed tai chi positively in the context of the variety of exercise regimens tested. However, although meta-analysis has confirmed the value of various types of exercises in preventing falls, tai chi has not yet been shown to be superior to other types of balance, strengthening, and endurance exercises.

The fact that fewer fall-prevention trials of all types have shown reduction in injurious falls than falls in general is mostly related to issues of sample size. Only about 10% to 15% of falls result in significant injury, and most fall-prevention trials were powered only to show reductions in total falls. Larger studies would probably have shown statistically significant reductions in injurious falls that paralleled the reduction in total falls.

Although we also agree with Dr. Pierre that exercise regimens introduced early in life will probably have lasting benefits into old age and will most likely increase the chance that older persons will remain active and fall-free, the evidence behind this assertion is thus far lacking in longitudinal or intervention trials. Nonetheless, we believe in the benefit of most forms of exercise at any age, not only for fall prevention but also for improving many other aspects of health and well-being.

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Alternative Medicine: A Mirror Image for Scientific Medicine

TO THE EDITOR: Vandenbroucke and de Craen should be congratulated for writing a stimulating article on medical thinking in general (1). I fear, however, that they may have gotten some of their specifics wrong when stating that homeopathy is supported by "seemingly solid evidence" (1). Vandenbroucke and de Craen base this statement on a meta-analysis by Linde and colleagues (2). However, several subsequent attempts (3, 4) to reanalyze Linde and colleagues' data set have cast considerable doubt on their positive conclusions. Most impressive, perhaps, Linde and colleagues themselves reanalyzed their data and concluded that "there was clear evidence that studies with better methodological quality tended to yield less positive results" (5). Thus, the trial evidence of homeopathy is not "seemingly solid" but seemingly unconvincing. In other words, Vandenbroucke and de Craen may be right about how doctors think but seem to be wrong about the clinical evidence regarding homeopathy.

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IN RESPONSE: We are grateful that Dr. Ernst points to new literature that includes reanalyses of the original meta-analysis on homeopathy by Linde and colleagues (1). However, in our paper, we already pointed to one reanalysis (2) that casts doubt on the robustness of the original. We also acknowledged that such reanalyses have been ongoing because scientists cannot believe the results of the original and therefore try to prove that the original was "methodologically flawed." Verdicts that a study (or a meta-analysis) is flawed are in this case based on reasoning and logic only because there is no "evidence" for "methodologic flaws."

This reasoning fits very well with the crossword analogy that we proposed. One entry in the crossword holds that infinite solutions cannot possibly have chemical activity; this entry is very well entrenched in physics, chemistry, and biology. In line with this entry, we prefer the entry interpreting the meta-analysis (or the original studies) as flawed, which has its own arguments embedded in reasoning and logic, as indicated by Dr. Ernst and others. Of course, this is not always immediately apparent. When the original meta-analysis on homeopathy was published, many were surprised and wondered whether there was anything in it. Gradually, however, it became clear that the findings were less robust than they originally were thought to be. In this way, all entries do now fit, and this "consilient" (3) fitting gives us an argument that endorses both methodologic and basic science reasoning.

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Clinical Inertia

TO THE EDITOR: After reading the Perspective by Phillips and colleagues on clinical inertia (1), I was inclined to agree that the desire of patients and physicians to "stay the course" when treating chronic illnesses often interferes with achieving excellent care. However, on further reflection, I felt that the paper greatly oversimplified many aspects of day-to-day medical practice.

Phillips and colleagues underestimated the extent, depth, and persistence of clinicians' discussions with patients and families about the benefits, risks, and costs of intensifying medical therapies for chronic diseases. Some patients with atrial fibrillation who are otherwise excellent candidates for anticoagulation decline it despite my best efforts at persuasion. Likewise, many diabetic patients opt to avoid the demands of more intense glycemic control, despite the attendant increased risks for hypoglycemia and weight gain. Because discussions about such decisions are ongoing and often span months and years, however, their depth may not be adequately reflected in chart notes. Over time, tolerance of the status quo may appear to an outside reviewer as "inertia."

I also feel that target or ideal values are too frequently viewed as the ultimate marker of successful treatment. Although these goals should be something to strive for, there is frequently a subtle or even overt sense that therapy will have little benefit unless the target is achieved. In fact, most of the important studies of glycemic control, lipid lowering, and hypertension treatment show that benefits are in large part linearly or progressively associated with improvement in the measured value. Having lowered a patient's low-density lipoprotein cholesterol level from 240 mg/dL to 140 mg/dL, we must often acknowledge that attempting to reduce it by 40 or 50 more points will greatly increase expense and risk for side effects. Is this "clinical inertia" or simply knowing when to stick with a pretty good hand?

In the end, my pendulum swung back slightly toward my original agreement that the desire to avoid upsetting the apple cart can and does sometimes hold us back. "Inertia," however, is a highly inaccurate characterization of the process.

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Reference

1. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. Ann Intern Med. 2001;135:825-34. [PMID: 11694107]

TO THE EDITOR: To be fair to the concept of inertia, best defined here as an indisposition to change, it should be acknowledged that inertia works in both directions. The attractive concept of clinical inertia proposed by Phillips and colleagues (1) should also encompass the failure of health care providers to stop or deescalate therapy. Treatment regimens too often contain medications that are continued indefinitely for little or no reason. Commonly encountered examples of lingering medications are gastric protective agents initiated long ago in the hospital for stress ulcer prophylaxis and hormone replacement therapy that no longer has clear-cut indications.

Reasons for this alternate direction of inertia parallel to that proposed by Phillips and colleagues include overestimation of the resources or adherence capacity of the patient, the use of "soft" reasons to avoid deescalating therapy, and the usual culprit: lack of adequate training or systems. This form of clinical inertia is partly responsible for the perception that physicians continue to add medicines with little consideration of cost or convenience to the patient regardless of whether there is supporting evidence. Failure to acknowledge this side of clinical inertia undermines the stewardship of resources that physicians are currently being asked to assume. For clinicians, the major point is that the patient's medication list is dynamic, and each medication should be scrutinized along with the patient in every clinical encounter.

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Reference

1. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. Ann Intern Med. 2001;135:825-34. [PMID: 11694107]

TO THE EDITOR: In the excellent article on clinical inertia by Phillips and colleagues (1), there is a section titled "Use of 'Soft' Reasons To Avoid Intensification of Therapy." I believe that the impact of such soft reasons cannot be overemphasized. As a practicing clinician, I can testify to the difficulty in getting patients to take medications for apparently asymptomatic conditions, as well as having patients continue to take such medications over the long haul. If long-term adherence to treatment is enhanced by obtaining patient "buy-in," then strategies employing nonmedication trials may delay reaching goal levels in the short run but may convince patients that medications are necessary and increase the likelihood of long-term adherence and treatment success. A major drawback to this strategy is that patients may quietly disappear from follow-up care.

Another underappreciated "soft" reason is side effects. If a drug has a side-effect rate similar to that of placebo, we think of it as innocuous and tolerable. However, if the placebo side-effect rate is

25% to 30%, then the patient has a substantial 25% to 30% higher likelihood of side effects (at least in the short term) with the drug than without it (and, of course, most drugs have side-effect rates higher than that of placebo). Finally, better patient education through mass media would make patients more receptive to treatment and indirectly diminish clinical inertia. For example, there is now a widespread belief that statins are dangerous drugs, making patient resistance to treatment worse than ever.

All of these factors contribute to patient reluctance to accept treatment. I believe that clinicians respond to this reluctance by prescribing more slowly (clinical inertia).

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IN RESPONSE: Our paper was prompted by observations that although many patients have chronic disorders that confer increased morbidity and mortality (1), they are often not managed to achieve the maximum potential benefit of therapy, despite strong evidence that treatment is beneficial and cost-effective and carries little major risk. In this context, Dr. Steinberg properly emphasizes that submaximal intensity of management may reflect the explicit wish of the patient. However, since national standards for care *can* be met in some real-world practice settings (2, 3), failure to meet such targets in other settings must be attributed either to patient self-selection bias or to insufficient emphasis by the physician: clinical inertia. Since emphasis on overcoming clinical inertia improved diabetes outcomes in our own practice without much in the way of patient objections or complications from hypoglycemia (3, 4), we believe that clinical inertia is often the limiting problem.

We agree that if the primary goal is no hypoglycemia or orthostatic hypotension, then glucose and blood pressure targets will often not be met. However, since such a posture is usually unreasonable, the question then becomes how to improve management. We must disabuse physicians of the notion that disorders are being treated adequately if they are treated at all; the combination of "suboptimal treatment" and "no complaints" may still be much less than what could be achieved in the same setting with little further increase in cost, inconvenience, or side effects. The responsibility for recommending intensification of management is the physician's, since only he or she can be fully informed about benefits and risks. We suspect that few physicians ask their patients specifically whether they would prefer a higher risk for stroke rather than a higher risk for orthostasis. We believe that rectifying the problem will require physician education in the details of treating to target, systems to show physicians exactly what their care consists of (since overestimation of performance is common [5]), and suggestions about ways to improve.

We agree with Dr. Wofford that periodic evaluations of medications are important. However, many patients will eventually need to be treated for combinations of diabetes *and* hypertension *and* dyslipidemia *and* heart failure *and* osteoporosis. Since management of these disorders is both evidence based and cost-effective, stopping appropriate therapy should not usually be considered until very late in life. Thus, for most patient encounters, the focus should properly be on doing more rather than doing less.

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Guidelines for the Management of Patients with Chronic Stable Angina

TO THE EDITOR: The guidelines for management of patients with chronic stable angina (1) represent an update from leading cardiology associations. Overall, the publication of these types of guidelines is useful for developing uniformity of practice when there is clear consensus due to high-quality, evidence-based clinical studies. The current applicability of such evidence, however, is often questioned. In particular, in these guidelines, the recommendations for revascularization in patients with left main, three-vessel disease, or two-vessel disease with involvement of the proximal left anterior descending artery are considered class I (evidence that treatment is useful) and grade A (high-quality data based on multiple randomized clinical trials). The supporting data, however, are too old to allow these recommendations to be uncritically adopted.

Current surgical recommendations are largely derived from data from the 1970s and 1980s (1), which precede current aggressive medical therapies for ischemia management (optimizing nitrates, β-blockers) and for risk factor reduction (especially cholesterol). Even the most recent study of surgical versus medical management, in the mid-1990s, did not have aggressive lipid lowering as a goal (2). Yet other data clearly show that aggressive lipid management leads to clear benefit within 6 months of initiating therapy (3, 4). In a study of patients with stable coronary artery disease in whom angioplasty was recommended, Pitt and colleagues (3) found that aggressive lipid lowering with 80 mg of atorvastatin decreased ischemic events by 36% over 18 months compared with angioplasty (3). By design, Pitt and colleagues' study excluded patients with left main or triple-vessel disease. Since no trial has compared present state-of-the-art medical management (especially aggressive lipid lowering) with surgery for these coronary lesions, which have higher mortality rates, recommendations for therapy should be tempered with the caveat that no clear current data are available.

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IN RESPONSE: Dr. Modest makes several valid points with which we concur. First, clinical practice guidelines must be continuously updated to reflect advances in knowledge. Second, data on the efficacy of coronary bypass surgery are relatively old and may not accurately reflect current practices and outcomes. Third, data are emerging to indicate that aggressive lipid-lowering therapy is an important component of regimens to manage symptoms of ischemia as well as to prevent future complications.

With regard to updating clinical guidelines, the American Heart Association and the American College of Cardiology require that updates and revisions be performed regularly. In fact, the guideline on the management of chronic stable angina by the American Heart Association, American College of Cardiology, and American College of Physicians–American Society of Internal Medicine, on which our article was based, is currently being updated. The rules require that any new information or recommendations included in the updated guidelines be based on high-quality evidence.

As Dr. Modest points out, some of the data from which recommendations for surgery are derived were collected in trials conducted over a decade ago, when results of both surgical and medical therapy were probably poorer than they are today. In keeping with our rules of evidence, however, these trials were methodologically sound and demonstrated important differences in mortality and control of symptoms for certain specific subgroups of patients. To date, these findings have not been supplanted by newer data from randomized trials, and a recent decision analysis indicates that there have been similar improvements in mortality due to advances in medical and surgical therapy for chronic stable angina (1). In our review, we specifically stated that such studies "must be interpreted cautiously," in part because "advances such as aggressive lipid lowering . . . were often not assessed" (2). As we also noted, similar concerns apply to comparisons of percutaneous coronary interventions because many earlier randomized trials did not incorporate the latest advances, such as intracoronary stents (with or without drug coating).

In reference to studies suggesting that aggressive lipid lowering may alleviate anginal symptoms, we share Dr. Modest's excitement. The major trial he cites, however, enrolled patients who were at very low risk for acute coronary events, had mainly absent or mild anginal symptoms, and would probably not have been candidates for surgery under any circumstances (3). Thus, the results of that trial have little relevance to recommendations for surgical intervention. Nonetheless, we share Dr. Modest's implied optimism that future trials involving higher-risk patients with more severe symptoms will show that aggressive medical therapy can obviate the need for invasive procedures in at least some patients.

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High-Dose Cyclophosphamide for Treatment of Aplastic Anemia

TO THE EDITOR: Brodsky and colleagues (1) assert that high-dose cyclophosphamide provides enduring remission from and even "cures" free from long-term complications in patients with severe aplastic anemia. However, a randomized trial by the U.S. National Institutes of Health (NIH) comparing antithymocyte globulin (ATG) with cyclophosphamide was terminated early because of unacceptable toxicity in the cyclophosphamide arm (2). This early termination, along with the subsequent observation of persistent paroxysmal nocturnal hemoglobinuria (PNH) clones, relapse, and evolution to cytogenetic abnormalities typical of myelodysplasia at similar rates in both arms (3), challenges Brodsky and colleagues' assertions.

Although Brodsky and colleagues report that PNH and myelodysplasia did not occur in their trial, they do not define these entities. Elsewhere, these authors previously reported the detection of PNH clones in most untreated patients with severe aplastic anemia and argued that clonality is an early event (4). Weren't such clones detected in the current series, and what was their fate after cyclophosphamide therapy? In addition, the determination of myelodysplasia requires frequent marrow examination and cytogenetic analysis. The cytogenetic abnormalities observed in our trial were among patients who remain in clinical remission. We are given few details of the early deaths in Brodsky and colleagues' study. In our trial, early deaths occurred exclusively in the cyclophosphamide arm, even in younger patients with adequate neutrophil counts at presentation; other patients were saved only by aggressive neutrophil transfusions.

These excess toxicities, along with the much higher requirements for supportive care related to the myelosuppressive effects of cyclophosphamide, were highly significant and clinically indisputable. They serve to point out that properly designed, conducted, and reported randomized, controlled trials are the best way to advance clinical practice while protecting the interests of research participants. The failure of cyclophosphamide to endure the rigors of our randomized, controlled trial was famously epitomized by the late Thomas Chalmers, who said, "One only has to review the graveyard of discarded therapies to discover how many patients have benefited from being randomly assigned to a control group" (5).

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IN RESPONSE: Over 15 years ago, a prospective, controlled study by Speck and colleagues suggested that antilymphocyte globulin was superior to allogeneic bone marrow transplantation for aplastic anemia (1). Initially embraced by many, the conclusions of this study have not stood the test of time, and bone marrow transplantation is now the preferred treatment for patients with matched siblings.

The randomized, controlled trial can be limited by the details of study design and execution. The NIH trial reported 6-month data on just 13 patients treated with cyclophosphamide and cyclosporine and just 12 patients treated with ATG and cyclosporine. The study accrued less than 20% of its planned enrollment and was terminated although neither rules for stopping nor primary or secondary end points were ever met. In addition, in contrast to our study, the NIH started cyclosporine concomitantly with cyclophosphamide and continued it for 6 months. The concomitant use of cyclosporine with cyclophosphamide may increase toxicity (2); furthermore, cyclosporine blocks the induction of tolerance, a potential mechanism of action for cyclophosphamide (3).

We found that high-dose cyclophosphamide alone leads to durable treatment-free remissions in most patients with aplastic anemia (4). Six patients from our initial trial (4) have remained in complete remission for more than 14 years, two for more than 20 years. The reported relapse rate for patients treated with ATG and cyclosporine in an earlier NIH series (5) was 50% at 5 years and 87% at 7 years. As we detailed in our report, all three deaths in our patients occurred among the nine who had very severe aplastic anemia. Such patients had an early mortality rate of 28% while taking ATG and cyclosporine in the NIH series. The survival rate in our patients is now 88.9% with no relapses, myelodysplasia, or PNH. All of the patients in our recent study are regularly screened for PNH or myelodysplasia. It is true that most patients with aplastic anemia harbor small PNH populations before treatment. We are monitoring these minute populations with highly sensitive assays, and so far they have regressed or remained stable.

Although the jury is still out on the role of high-dose cyclophosphamide in aplastic anemia, we hope the NIH group does not believe that the results of a small trial combining cyclosporine with cyclophosphamide and having only short follow-up should halt further study on this promising treatment approach. Over 15 years ago, because of the high rate of late complications (relapse and secondary clonal disorders) in patients with aplastic anemia who received antilymphocyte globulin, Speck and colleagues recommended continued study of bone marrow transplantation.

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Postoperative Pulmonary Complications

TO THE EDITOR: Arozullah and colleagues (1) describe the development of a multifactorial risk index for the prediction of postoperative pneumonia. The accompanying editorial by Lawrence (2) discusses the authors' decision to use a homogeneous outcome variable (postoperative pneumonia), in contrast to previous studies that used less clearly defined postoperative pulmonary complications as outcome measures. I take issue with the description of hypoxemia as a postoperative complication of "little clinical significance."

Eichhorn (3) has reviewed the importance of late desaturation and hypoxemia. There are two recognized patterns: persistent hypoxemia, which is related to preoperative respiratory function, and episodic nocturnal hypoxemia, which is closely related to episodic sleep apnea and is aggravated by postoperative physiologic disturbances. The latter form of hypoxemia has in particular been linked with possible organ dysfunction and subsequent morbidity and possibly mortality. Episodic nocturnal hypoxemia has been associated with episodes of cardiac ischemia and may contribute to the increased frequency of unexpected postoperative deaths noted at night.

A second point worthy of mention is the recent evidence showing not only that avoidance of hypoxemia is desirable but also that supplemental oxygen in the early postoperative period may improve outcome. Supplemental perioperative oxygen has been shown to reduce the incidence of surgical wound infections (4) and of postoperative nausea and vomiting (5) in patients undergoing colorectal surgery. The mechanism underlying this improvement is unknown but is thought to be related to improved tissue oxygenation and thus avoidance of subtle tissue ischemia.

Postoperative hypoxia is associated with increased morbidity and mortality, and avoidance of subtle tissue ischemia with supplemental oxygen improves outcome in terms of reduced wound infections and postoperative nausea and vomiting. To suggest that postoperative hypoxemia is of little clinical insignificance is to trivialize a potentially serious postoperative complication that is amenable to a simple and cheap preventive measure, namely the administration of supplemental oxygen in the postoperative period.

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IN RESPONSE: Measurement of oxygenation, purely numerically, as a surrogate, without clear linkage to clinically important outcomes, may not advance the science or art of patient care and research in perioperative pulmonary risk management. Data from a large trial of pulse oximetry in the operating room and postanesthesia care unit suggest that there is more measurable hypoxemia than there are important clinical sequelae of it (1). Mild hypoxemia, which probably has little clinical significance as a postoperative pulmonary complication, should not be considered as such in the same league as pneumonia.

There may be other reasons to care about oxygenation besides pulmonary complications. Dr. Ramsay cites two reports from a multicenter trial of patients having colorectal surgery who were randomly assigned to receive 30% (standard care) or 80% supplemental oxygen intraoperatively and 2 hours postoperatively (2, 3). Eighty percent supplemental oxygen was associated with less postoperative nausea and vomiting and fewer wound infections (2, 3). Both reports state that oxygen saturation was maintained at greater than 92% to at least 95% in all patients.

Dr. Ramsay's mention of "subtle tissue ischemia" provides additional perspective. The definition of clinically important hypoxemia may vary among tissues. In the study of wound infection (3), mean arterial oxygen saturation was 98.7% and 99.7% in the 30% and 80% oxygen groups, respectively. The difference between these groups was statistically significant ($P < 0.001$), but would anyone argue that it is clinically important? Yet clinical meaning is less clear for the similarly statistically significant differences between groups for more sophisticated measures of intraoperative tissue oxygenation: mean subcutaneous oxygen tension (59 mm Hg vs. 109 mm Hg), muscle oxygen tension (25 mm Hg vs. 40 mm Hg), and partial pressure of arterial oxygen (121 mm Hg vs. 348 mm Hg). Do the latter measures validly lower the bar for "clinical" hypoxemia, or are they irrelevant surrogate measures? It takes well-designed research that defines the link between surrogate measures and clinical outcomes to answer these questions.

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RESEARCH LETTERS

Permanent Paralysis of the Right Phrenic Nerve

TO THE EDITOR: Although right phrenic nerve paralysis is an acknowledged immediate complication of implanted venous access portals, it has only recently been recognized as a late sequela of this device. To a growing list of similar occurrences, we add this case report of a 44-year-old woman with infiltrating ductal carcinoma of the breast, treated with 5-fluorouracil, cyclophosphamide, and doxorubicin chemotherapy as a continuous 48-hour infusion through a Hickman catheter. Eighty days after successful implantation of a right subclavian venous catheter, the patient developed right shoulder pain. Plain chest radiography and venography documented a widened mediastinum, raised right hemidiaphragm, and thrombosis of the superior vena cava without dye extravasation. Despite resolu-

Table. **Permanent Paralysis of the Right Phrenic Nerve Related to Central Venous Catheters***

Study (Reference)	Year	Central Venous Access Device	Disease	Treatment	Sample Size, *n*	Mean Time to Event, *d*	Thrombosis?	Pain?
Munzone et al. (3)	2000	Implanted port	Breast cancer	Chemotherapy infusion	15	108	NR in 15 patients	Yes (14 of 15 patients)
Aggarwal et al. (1)	2000	Double-lumen catheter	Renal failure	Hemodialysis	1	90	Yes (1 of 1 patient)	No (0 of 1 patient)
Rigg et al. (4)	1997	Hickman catheter	Colorectal cancer	Chemotherapy infusion	5	93	Yes (4 of 5 patients)	Yes (5 of 5 patients)
Leong et al. (2)	1996	Hickman double-lumen catheter	Myeloma	Chemotherapy infusion	1	60	Yes (1 of 1 patient)	Yes (1 of 1 patient)

* NR = not reported.

tion of the thrombus with therapeutic anticoagulation, the hemidiaphragm has remained paralyzed.

The **Table** summarizes the 22 cases in the international literature of permanent right phrenic nerve paralysis due to late complication of indwelling central venous catheters. Various right- and left-sided catheters were used for hemodialysis (1) or systemic chemotherapy with a variety of chemotherapeutic agents (2–4). Average time to right phrenic nerve paralysis was approximately 3 months. Right shoulder pain was a prominent symptom in all but one case (1). Thrombosis was important in three reports (1, 2, 4) as well as in our case but was not mentioned in the largest series (3). Prophylactic warfarin was not preventive (4). We speculate that venous wall damage resulting from inflammation associated with thrombus formation caused phrenic nerve paralysis.

Since the use of indwelling central venous catheters has increased dramatically during the past decade, this phenomenon could be more frequent in the future. Perhaps with early detection and treatment, this event would be reversible. We therefore suggest heightened suspicion for phrenic nerve paralysis as a potential late complication of central venous catheters, usually in conjunction with right shoulder pain and thrombosis formation.

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Diagnosis by Death

TO THE EDITOR: A 40-year-old previously healthy Chinese woman presented with progressive right thigh pain for 10 days. Her medical history was unremarkable except for menorrhagia since menarche, for which she irregularly took iron tablets prescribed by her family physician. Physical examination showed pallor. Passive straight-leg raising was reduced to 45 degrees on the right side, limited by pain radiating from the posterior thigh to the posterior and lateral aspect of the leg, with Lasègue sign. Blood pressure was 125/80 mm Hg, and pulse was sinus at 84 beats/min. Other physical findings were normal. Hemoglobin level was 71 g/L, mean corpuscular volume was 69 fL, leukocyte count was 13×10^9 cells/L, and platelet count was 35×10^9 cells/L. Serum sodium level was 140 mmol/L, potassium level was 3.9 mmol/L, creatinine concentration was 95 µmol/L (1.1 mg/dL), alkaline phosphatase level was 2.15 nkat/L (normal range, 0.93 to 1.98 nkat/L), hepatic aminotransferase levels were just above the upper limits of normal, bilirubin level was 16 µmol/L (0.94 mg/dL), and γ-glutamyltranspeptidase level was 50 IU/L (normal range, 7 to 32 IU/L). Results of radiography of the lumbosacral spine were normal. The patient received a transfusion but developed sudden hemodynamic collapse and died. Postmortem examination revealed ruptured hepatocellular carcinoma and positive results on tests for hepatitis B surface antigen.

Hepatocellular carcinoma is prevalent in southeast Asia, where hepatitis B virus infection is endemic (1). Its presentation ranges from incidental finding on surveillance detection (2) to spontaneous rupture causing acute hemoperitoneum and hypovolemic shock (3). Subclinical rupture of hepatocellular carcinoma is often difficult to diagnose. Sciatica as an initial manifestation has not been reported before to our knowledge and is certainly uncommon. Its presence in association with unexplained anemia, mild liver function derangement, and the hepatitis B carrier state should arouse suspicion of subclinical bleeding causing nerve-root irritation to the lumbosacral region. Early detection of hepatocellular carcinoma would allow lifesaving means of hemostasis, such as hepatic arterial embolization or staged hepatic resection (4).

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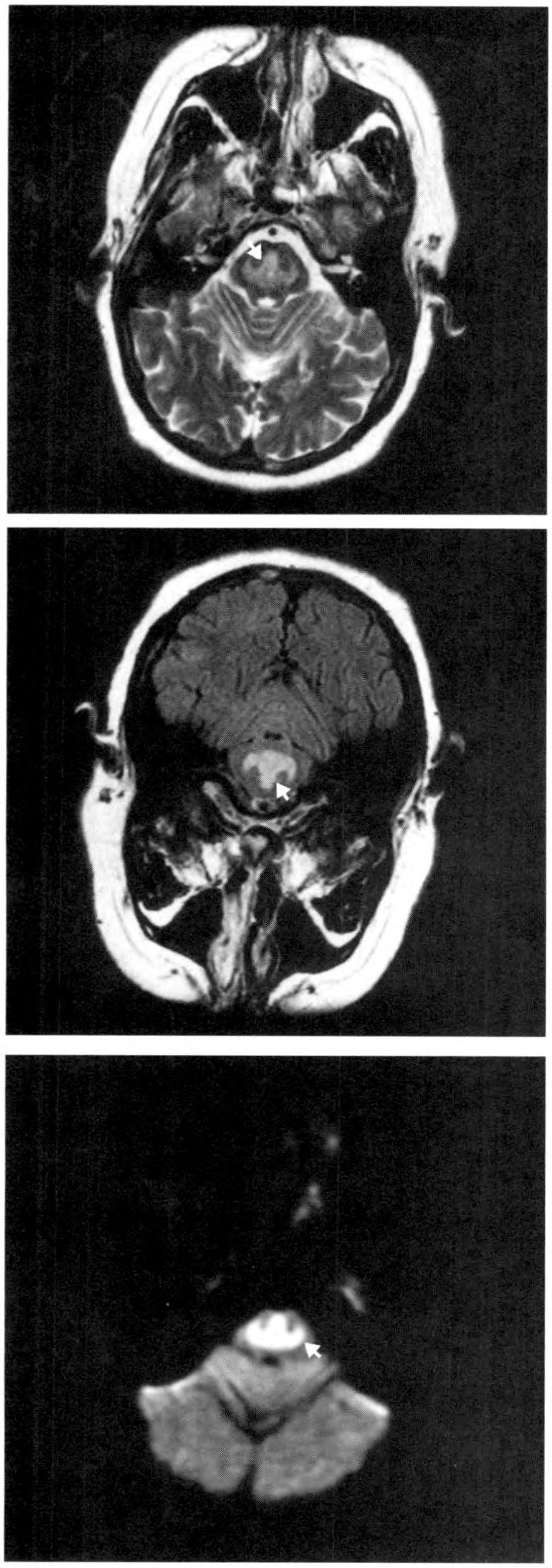
Figure. **Findings on magnetic resonance imaging.**



Top. Axial T2-weighted image through the brainstem. **Middle.** Fluid-attenuated inversion recovery image through the brainstem. **Bottom.** Diffusion-weighted image. Arrows indicate a process compatible with central pontine myelinolysis.

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Central Pontine Myelinolysis

TO THE EDITOR: A 42-year-old woman receiving hydrochlorothiazide for hypertension presented with nausea, vomiting, diarrhea, shock, and dehydration after binge drinking of vodka and mixed hard liquor. Serum sodium level at admission was 97 mmol/L; the patient required 4 L of intravenous normal saline infusion to achieve hemodynamic stability. Serum sodium level gradually normalized within the next 4 days (<1 L of sodium correction per hour), but the patient's course was complicated over the next 7 days by dysarthria, mutism, facial and neck weakness, and profound quadriparesis with spastic flexion of the lower limbs and Babinski signs.

On magnetic resonance imaging, an axial T2-weighted scan (**Figure**, *top*) and a fluid-attenuated inversion recovery scan (**Figure**, *middle*) through the brainstem demonstrated striking abnormal signal consistent with edema in the central tracts of white matter. Additional diffusion-weighted imaging (**Figure**, *bottom*) revealed abnormal signal consistent with restricted diffusion, implying an acute process compatible with central pontine myelinolysis.

Khosrow Afsari, MD
Touro University College of Osteopathic Medicine
San Pablo, CA 94806

Jonathan P. Posin, MD
University of California, San Francisco
Pinole, CA 94564

CORRECTION

Correction: Identification of Persons at High Risk for Type 2 Diabetes Mellitus

In an article on the identification of persons at high risk for type 2 diabetes mellitus (1), the formula in the Appendix on page 581 contained an error. The formula should read $p = 1/(1 + e^{-x})$ rather than $p = 1/(1 - e^{-x})$.

Reference

1. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? Ann Intern Med. 2002; 136:575-81. [PMID: 11955025]

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. Order phone numbers and Web sites can be used to place orders directly with publishers.

Medical Management of Diabetes and Heart Disease

Sobel BE, Schneider DJ, eds. 292 pages. New York: Marcel Dekker; 2002. $125.00. ISBN 0824707451. Order phone 212-696-9000.

Field of medicine: Endocrinology and cardiology.

Format: Hardcover book.

Audience: Specialists and primary care physicians who manage patients with diabetes. House officers and nonphysician providers will also find the book insightful regarding the complex link between diabetes and cardiovascular disease.

Purpose: To provide the reader with an understanding of the pathophysiology of diabetic heart disease, to develop risk reduction strategies, and to provide drug and nondrug management options for the common cardiovascular complications of diabetes.

Content: The book contains 16 chapters. The first chapter summarizes the metabolic defects of diabetes that contribute to cardiovascular disease and discusses targeted treatment strategies. The remaining chapters address cardiovascular disease in type 1 and type 2 diabetes; insulin resistance; syndrome X; hypertension, dyslipidemia, and the coagulation–fibrinolytic system as contributing factors; the polycystic ovary syndrome; detection and diagnosis of heart disease; the management of diabetes and comorbid cardiovascular disease; the risks and benefits of coronary revascularization; and nondrug risk reduction strategies and targets for future therapies.

Highlights: The book is appropriate for both veteran and less experienced clinicians. The chapters are pertinent, well written, easy to understand, and amply referenced or cross-indexed. The book's strength lies in the authors' attention to blending present-day basic science and clinical research data to explain the complex relationships shaping the development of diabetic cardiovascular disease. The chapter on coronary revascularization is particularly noteworthy.

Limitations: Despite its title, the book is primarily devoted to characterizing the pathophysiologic basis for diabetic heart disease. Inconsistent attention is given to specific therapeutic, dosing, and monitoring issues or recommendations. Several of the figures require enlargement or revision to enhance understanding (for example, figure 3 on page 40; figure 1 on page 234). On page 77, it's stated that β-blockers can "also cause *vasospasm* in asthmatic patients," an obvious confusion with *bronchospasm.* Since the book's publication, several research trials and guidelines have been published or changed. This new information could affect interpretation of the book's present recommendations (for example, blood pressure goals).

Related reading: The only comparable secondary reference is Garber's "Type 2 Diabetes" in *Endocrinology and Metabolism Clinics of North America* (WB Saunders, 2001). Although the subject matter of that book is more diverse, the contributing authors address many of the same issues. Given the shortcomings of published reference textbooks, the primary literature remains the best option for readers who want to stay current with the changing landscape of diabetes and heart disease.

Reviewer: Charles D. Ponte, PharmD, Departments of Clinical Pharmacy and Family Medicine, West Virginia University, Schools of Pharmacy and Medicine, Morgantown, West Virginia.

Blackwell's Primary Care Essentials: Travel Medicine

Smith RP, Sears ST. 299 pages. Malden, MA: Blackwell Science; 2002. $39.95. ISBN 0632044829. Order phone 800-216-2522.

Field of medicine: Ambulatory and general medical care.

Format: Softcover book (pocket-size).

Audience: Primary care and emergency medicine physicians and nurse practitioners caring for travelers.

Purpose: To serve as a ready reference for medical providers preparing travelers for trips and evaluating travelers upon return.

Content: This is the seventh publication of 10 planned volumes of Blackwell's Primary Care Essentials series. The handbook is divided into a section on prevention and a larger section on the diagnosis and management of travel-related illness. Brief appendices related to antiparasitic drugs and bibliographic references including Web sites are provided.

Highlights: The book provides well-focused, succinct, and relatively encyclopedic coverage of the before-and-after aspects of travel medicine for providers needing a handy, easily accessible pocket guide.. As with other volumes in the series, each of the more than 150 individual subject areas begins with one or more up-to-date literature references to facilitate gathering information expeditiously. The area on prevention issues is particularly useful in providing information related to special-needs travelers, such as those who are pregnant or immunosuppressed. The book provides good coverage of prevention of environmental illnesses, such as marine envenomations, while still covering the basics related to prevention of travel-related infectious diseases.

Limitations: The depth of information covered is understandably limited in a handbook, and this problem is most evident in the diagnosis and treatment section of the book, which provides information on 109 infectious diseases. Although the information specifically related to travel-associated diseases is useful and worthwhile, the inclusion of some subjects, such as toxic shock syndrome, skin and soft tissues infections, and pneumococcal infections, is unnecessary and limits the depth of other, more relevant areas.

Related reading: In the preface, the authors urge readers to consider the handbook as an adjunct to information garnered from the Centers for Disease Control and Prevention and other travel medicine Web sites. Guerrant and colleagues' *Tropical Infectious Disease: Principles, Pathogens, and Practice* (Churchill Livingstone, 1999) is the standard comprehensive reference in the field.

Reviewer: Philip C. Carling, MD, Infectious Diseases Section, Carney Hospital, Boston, Massachusetts.

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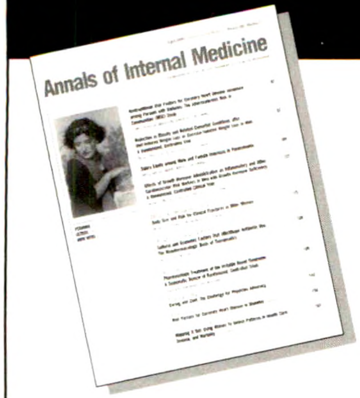

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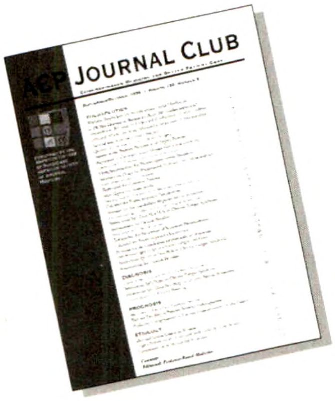

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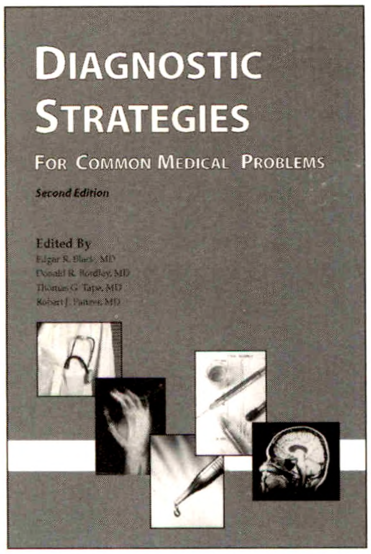

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A 45-year-old woman presents with weight loss of approximately 9 kg (20 lb) over the past 12 months. She has been aware of no change in appetite. She eats three meals daily and snacks most evenings. Her activity has similarly been unchanged. She exercises by walking 2 to 3 miles three or four times weekly. She takes no medication and reports no alcohol or drug use. Review of systems reveals a 1- to 1.5-year history of a pruritic rash on the trunk and extremities. She reports occasional vague abdominal pain and bloating, which subside spontaneously in a few hours, and notes the passage of flatus. She has no food intolerance, difficulty swallowing, sweating, tremor, constipation, diarrhea, or arthritis. She has normal, regular menstrual periods and has two to three stools per day, with no recent change.

The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 ˚C (98.4 ˚F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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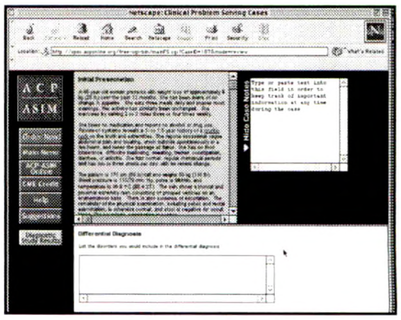

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Community-dwelling elderly persons, especially those with impaired left ventricular function, have a substantial risk for death from congestive heart failure. However, more deaths occur from heart failure in persons with normal systolic function because left ventricular function is more often normal than impaired in elderly persons with heart failure.

Short-Course Rifampin and Pyrazinamide Compared with Isoniazid for Latent Tuberculosis Infection: A Multicenter Clinical Trial 640

R.M. Jasmer, J.J. Saukkonen, H.M. Blumberg, C.L. Daley, J. Bernardo, E. Vittinghoff, M.D. King, L.M. Kawamura, and P.C. Hopewell, for the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators

A 2-month regimen of rifampin and pyrazinamide for latent tuberculosis infection was associated with an increased risk for grade 3 or 4 hepatotoxicity compared with a 6-month regimen of isoniazid. Liver enzymes should be measured routinely during treatment to screen for liver injury and prevent progression to severe toxicity.

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J.L. Gerberding

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R.K. Schneider and J.L. Levenson

This Update covers mood disorders, anxiety disorders, medical–psychiatric comorbid conditions, and cognitive disorders.

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DOCUMENTS CITED

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Annals of Internal Medicine | ARTICLE

Outcome of Congestive Heart Failure in Elderly Persons: Influence of Left Ventricular Systolic Function

The Cardiovascular Health Study

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Gerard P. Aurigemma, MD; and Teri A. Manolio, MD, MHS

Background: Most persons with congestive heart failure are elderly, and many elderly persons with congestive heart failure have normal left ventricular systolic function.

Objective: To evaluate the relationship between left ventricular systolic function and outcome of congestive heart failure in elderly persons.

Design: Population-based longitudinal study of coronary heart disease and stroke.

Setting: Four U.S. sites: Forsyth County, North Carolina; Sacramento County, California; Allegheny County, Pennsylvania; and Washington County, Maryland.

Participants: 5888 persons who were at least 65 years of age and were recruited from the community.

Measurements: Total mortality and cardiovascular morbidity and mortality.

Results: Of 5532 participants, 269 (4.9%) had congestive heart failure. Among these, left ventricular function was normal in 63%, borderline decreased in 15%, and overtly impaired in 22%. The mortality rate was 25 deaths per 1000 person-years in the reference group (no congestive heart failure and normal left ventricular function at baseline); 154 deaths per 1000 person-years in participants with congestive heart failure and impaired left ventricular systolic function; 87 and 115 deaths per 1000 person-years in participants with congestive heart failure and normal or borderline systolic function, respectively; and 89 deaths per 1000 person-years in persons with impaired left ventricular function but no congestive heart failure. Although the risk for death from congestive heart failure was lower in persons with normal systolic function than in those with impaired function, more deaths were associated with normal systolic function because more persons with heart failure fall into this category.

Conclusions: Community-dwelling elderly persons, especially those with impaired left ventricular function, have a substantial risk for death from congestive heart failure. However, more deaths occur from heart failure in persons with normal systolic function because left ventricular function is more often normal than impaired in elderly persons with heart failure.

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Congestive heart failure is the most frequent cause of hospitalization in persons 65 years of age or older, accounting for more than 875 000 admissions each year in the United States (1). Moreover, aging of the population, increased susceptibility of elderly hypertensive persons to congestive heart failure (2), decreasing incidence of and death from stroke, and improved survival after acute myocardial infarction have increased the number of patients at risk for congestive heart failure (1, 3, 4).

The clinical syndrome of congestive heart failure occurs over a broad range of underlying left ventricular systolic function (5–7). Compared with persons younger than 65 years of age, more elderly persons with congestive heart failure have normal systolic function (5, 8). Elevated pulmonary venous pressure, which accounts at least in part for the clinical manifestations of congestive heart failure, is likely to result from impaired diastolic ventricular filling (9). This impairment may be the consequence of diminished systolic function or of other causes (10–14) that may result in decreased myocardial compliance in the absence of systolic dysfunction.

The probability of survival diminishes substantially after congestive heart failure is diagnosed (15, 16). However, studies have differed about the impact of left ventricular systolic function on survival (17–23). We tested the hypothesis that congestive heart failure confers increased morbidity and mortality in elderly persons even in the presence of normal or only mildly impaired left ventricular systolic function. We also hypothesized that impaired systolic function would be independently associated with greater risk than normal or borderline function.

METHODS

Study Sample

The Cardiovascular Health Study, designed to assess cardiovascular disease, cardiovascular disease outcomes, and risk factors, identified adults from the Health Care Financing Administration Medicare enrollment lists in four widely separated U.S. communities, along with other household members who were older than 65 years of age at study enrollment. Recruitment centers were located in Washington County, Maryland; Forsyth County, North Carolina; Sacramento County, California; and Allegheny County, Pennsylvania. Persons were excluded from the Cardiovascular Health Study if they were receiving active treatment for cancer, were wheelchair-bound or institutionalized, or were unable to participate in the examination. Prevalent coronary artery disease, stroke, and heart failure were not exclusion criteria. When we included both

Context

Most patients with congestive heart failure (CHF) are 65 years of age or older.

Older patients more often have CHF with normal left ventricular systolic function than younger patients.

How left ventricular systolic function affects prognosis of CHF in older patients is not clear.

Contribution

In this population-based study of 5532 older adults, 4.9% had CHF with normal (63%), borderline decreased (15%), or impaired (22%) left ventricular systolic function.

Forty-five percent of those with CHF and 16% of those without CHF died within 6 to 7 years.

Among those with CHF, death rates were higher with decreased versus normal left ventricular systolic function.

–The Editors

the original cohort (recruited in 1989 to 1990) and those enrolled when the study was expanded to include more African-American persons (in 1992 to 1993), data were available from 5888 study participants. Details of the design, sampling, and recruitment of the Cardiovascular Health Study, as well as the interview and examination, have been published previously (24). Self-report of cardiovascular and pulmonary diseases was validated according to standardized criteria through assessment of medications, medical records, and relevant information obtained during the initial examination. Further evaluation involved fasting blood chemistry tests, measurement of blood pressure and heart rate, anthropometric measurements, electrocardiography, echocardiography, carotid ultrasonography, and other objective measurements. Participants without an interpretable echocardiogram and those with significant aortic or mitral stenosis, greater than moderate mitral regurgitation, or at least moderately severe aortic regurgitation were excluded from our study.

Adjudication of Congestive Heart Failure

Details of the methods used to assess the prevalence of congestive heart failure among participants in the Cardiovascular Health Study have been reported previously (25, 26). An expert panel adjudicated the index event of congestive heart failure by reviewing all pertinent data on the hospitalization or outpatient visit, including history, physical examination, report of chest radiography, and medication usage. Self-report of a physician diagnosis of congestive heart failure was confirmed by documentation in the medical record of a constellation of symptoms (shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (edema, pulmonary rales, gallop rhythm, displaced left ventricular apical impulse) or by supporting clinical findings, such as those on chest radiography. Diagnosis of congestive heart failure was also confirmed if, in addition to having a previous physician diagnosis, the participant was receiving medical therapy for congestive heart failure (a current prescription of a diuretic and digitalis or a vasodilator [nitroglycerin, hydralazine, or angiotensin-converting enzyme inhibitor]).

Adjudication of Outcome Events

Throughout the follow-up period, participants were interviewed every 6 months and follow-up examinations

Table 1. **Baseline Characteristics of Participants by Study Group***

Characteristic	No CHF, Normal LV Systolic Function (n = 4864)	No CHF, Borderline LV Systolic Function (n = 263)	No CHF, Impaired LV Systolic Function (n = 136)
Age, *y*	72.7 ± 5.5	73.9 ± 6.1	74.5 ± 5.7
Men, *n (%)*	1940 (39.9)	170 (64.6)	101 (74.3)
African-American ethnicity, *n (%)*	613 (12.6)	30 (11.4)	15 (11.0)
Weight, *kg*	72.1 ± 14.3	77.2 ± 14.3	77.0 ± 14.2
Systolic blood pressure, *mm Hg*	135.9 ± 21.3	136.0 ± 20.4	138.2 ± 23.3
Diastolic blood pressure, *mm Hg*	70.7 ± 11.1	70.4 ± 12.6	72.5 ± 12.5
Hypertension, *n (%)*	2195 (45.1)	148 (56.3)	63 (46.3)
Diabetes, *n (%)*	518 (10.7)	48 (18.3)	21 (15.4)
Coronary heart disease, *n (%)*	725 (14.9)	92 (35.0)	79 (58.1)
Serum creatinine concentration, *µmol/L (mg/dL)*	91 ± 27 (1.03 ± 0.3)	106 ± 53 (1.20 ± 0.6)	108 ± 35 (1.22 ± 0.4)
Serum cholesterol level, *mmol/L (mg/dL)*	5.5 ± 1.0 (212.6 ± 38.7)	5.4 ± 1.0 (207.0 ± 40.1)	5.2 ± 1.0 (202.9 ± 41.6)
FEV_1, *L/min*	2.07 ± 0.7	2.14 ± 0.7	2.14 ± 0.7
Ankle–arm index < 0.9, *n (%)*	535 (11.0)	42 (16.0)	38 (27.9)
Alcohol intake, *drinks/wk*	2.51 ± 6.3	3.26 ± 7.7	1.92 ± 5.3
Internal carotid intima–media thickness, *mm*	1.41 ± 0.6	1.58 ± 0.6	1.74 ± 0.6
Common carotid intima–media thickness, *mm*	1.05 ± 0.2	1.11 ± 0.3	1.16 ± 0.2
Atrial fibrillation on electrocardiography, *n (%)*	86 (1.8)	13 (4.9)	9 (6.6)
Early mitral inflow velocity on Doppler ultrasonography, *cm/s*	71 ± 17	69 ± 20	65 ± 19
Late mitral inflow velocity on Doppler ultrasonography, *cm/s*	80 ± 22	80 ± 25	76 ± 28
Ratio of early to late mitral inflow velocity	1.25 ± 5.0	0.98 ± 0.8	1.42 ± 3.0
LV mass on electrocardiography, *g*	150.3 ± 29.5	171.4 ± 38.1	185.3 ± 40.7
Mitral regurgitation, *n (%)*	329 (6.8)	24 (9.1)	19 (14.0)

* Values presented with plus/minus sign are the mean ± SD. Differences in all variables among the six groups (except late mitral inflow velocity) were statistically significant for unadjusted analyses and for analyses adjusted for age and sex ($P < 0.01$). CHF = congestive heart failure; LV = left ventricular.

were conducted annually at each local center. Outcome events were tabulated on the basis of report of physician-diagnosed myocardial infarction or stroke and were then confirmed as described earlier. Deaths were confirmed by review of medical records and death certificates, as well as review of data on hospitalizations from the Health Care Financing Administration Medicare database on health care utilization. Cardiovascular death was classified according to criteria published previously (27). Briefly, myocardial infarction, stroke, sudden cardiac death, aortic aneurysm, peripheral vascular disease, mesenteric events, and congestive heart failure were included as immediate causes of death. Through these methods, as well as through interviews of contacts and proxies for participants lost to follow-up, we accounted for vital status in 100% of our participants.

Echocardiography and Left Ventricular Systolic Function

The design for echocardiographic study of participants in the Cardiovascular Health Study has been published previously (28). Briefly, two-dimensional echocardiography was performed at the baseline visit for the original cohort and at 2 years after the baseline visit for the second cohort. All echocardiograms were interpreted at a centralized core echocardiography laboratory by persons blinded to participants' clinical information. To avoid lost statistical power due to an inability to determine left ventricular mass on echocardiography in a substantial number of participants, left ventricular mass was estimated by electrocardiography using methods published elsewhere (29). Valvular regurgitation and stenosis were assessed as previously described (28). Global left ventricular systolic function was qualitatively assessed on two-dimensional echocardiography as normal, borderline, or impaired, corresponding to an ejection fraction of 0.55 or greater, 0.45 to 0.54, and less than 0.45, respectively. Qualitative systolic function was assessable in 5649 (96%) of the original and second Cardiovascular Heath Study cohorts. The interreader agreement was 95% ($\kappa = 0.32$) based on quality-control rereads of 370 study echocardiograms, and the intrareader agreement was 99% in 158 rereads ($\kappa = 0.92$) (30).

Clinical Assessment and Measurements

At study enrollment, clinically evident coronary artery disease was determined as described previously (24–26). Diabetes mellitus was defined according to history reported on the questionnaire and current use of insulin or oral hypoglycemic medication. The ankle–arm index (the ratio of supine systolic blood pressure at the ankle to that at the brachial artery, a measure of lower-extremity arterial occlusive disease [31]) was measured at baseline in both the original and second cohort. Baseline analyses of fasting serum chemistry values and fasting lipid measurements were also performed for both cohorts. Measures of pulmonary function, performed at the baseline visit for the original cohort and at 1 year after the baseline visit for the second cohort, included FVC and FEV_1. At the baseline visit for both cohorts, common and internal intima–media thickness of the carotid artery was measured. Digitally recorded twelve-lead electrocardiograms, obtained at the baseline examination for both cohorts, were analyzed as described elsewhere (25, 26).

Study Groups

To evaluate the relationship between left ventricular systolic function and outcome of congestive heart failure,

Table 1—**Continued**

CHF, Normal LV Systolic Function (*n* = 170)	CHF, Borderline LV Systolic Function (*n* = 39)	CHF, Impaired LV Systolic Function (*n* = 60)
74.8 ± 6.0	73.2 ± 6.0	74.0 ± 5.5
75 (44.1)	19 (48.7)	38 (63.3)
32 (18.8)	10 (25.6)	14 (23.3)
75.5 ± 17.7	77.0 ± 17.4	74.6 ± 14.5
137.9 ± 26.8	136.3 ± 20.6	126.6 ± 22.0
67.8 ± 13.4	67.7 ± 12.2	66.1 ± 12.3
101 (59.4)	28 (71.8)	34 (56.7)
45 (26.5)	14 (35.9)	14 (23.3)
98 (57.6)	27 (69.2)	47 (78.3)
106 ± 44 (1.20 ± 0.5)	103 ± 27 (1.16 ± 0.3)	137 ± 8 (1.55 ± 1.1)
5.0 ± 0.9 (197.1 ± 38.2)	5.2 ± 1.1 (202.9 ± 43.3)	5.1 ± 1.1 (200.3 ± 44.1)
1.75 ± 0.6	1.77 ± 0.5	1.96 ± 0.6
39 (22.9)	10 (25.6)	18 (30.0)
1.50 ± 5.0	2.11 ± 6.8	0.76 ± 3.1
1.64 ± 0.6	1.70 ± 0.7	1.80 ± 0.7
1.11 ± 0.2	1.11 ± 0.2	1.14 ± 0.3
25 (14.7)	5 (12.8)	3 (5.0)
78 ± 27	83 ± 30	77 ± 34
77 ± 33	84 ± 33	82 ± 34
2.62 ± 8.6	2.55 ± 6.3	1.91 ± 4.9
162.6 ± 36.7	175.2 ± 32.0	219.5 ± 77.3
16 (9.4)	9 (23.1)	15 (25.0)

Table 2. **Medication Use by Study Group***

Group (Participants)†	β-Blockers‡	ACE Inhibitors§	Lipid-Lowering Drugs‖	Diuretics§	Calcium-Channel Blockers§	Frequent Aspirin Use§¶	Digitalis§
	←			n (%)			→
Study subgroups							
No CHF, normal LV systolic function (*n* = 4862)	607 (12.5)	303 (6.2)	263 (5.4)	1282 (26.4)	574 (11.8)	1138 (23.4)	283 (5.8)
No CHF, borderline LV systolic function (*n* = 261)	46 (17.6)	27 (10.3)	14 (5.4)	79 (30.3)	50 (19.2)	71 (27.2)	26 (10.0)
No CHF, impaired LV systolic function (*n* = 136)	20 (14.7)	12 (8.8)	11 (8.1)	42 (30.9)	30 (22.1)	43 (31.6)	26 (19.1)
CHF, normal LV systolic function (*n* = 170)	29 (17.1)	42 (24.7)	8 (4.7)	100 (58.8)	52 (30.6)	63 (37.1)	70 (41.2)
CHF, borderline LV systolic function (*n* = 39)	3 (7.7)	11 (28.2)	1 (2.6)	29 (74.4)	18 (46.2)	18 (46.2)	18 (46.2)
CHF, impaired LV systolic function (*n* = 60)	4 (6.7)	25 (41.7)	1 (1.7)	47 (78.3)	18 (30.0)	25 (41.7)	31 (51.7)
Alternate subgroups							
No CHF (*n* = 5259)	673 (12.8)	342 (6.5)	288 (5.5)	1403 (26.7)	654 (12.4)	1252 (23.8)	335 (6.4)
CHF (*n* = 269)	36 (13.4)	78 (29.0)	10 (3.7)	176 (65.4)	88 (32.7)	106 (39.4)	119 (44.2)
Normal LV systolic function (*n* = 5032)	636 (12.6)	345 (6.9)	271 (5.4)	1382 (27.5)	626 (12.4)	1201 (23.9)	353 (7.0)
Borderline LV systolic function (*n* = 300)	49 (16.3)	38 (12.7)	15 (5.0)	108 (36.0)	68 (22.7)	89 (29.7)	44 (14.7)
Abnormal LV systolic function (*n* = 196)	24 (12.2)	37 (18.9)	12 (6.1)	89 (45.4)	48 (24.5)	68 (34.7)	57 (29.1)

* ACE = angiotensin-converting enzyme; CHF = congestive heart failure; LV = left ventricular.

† For 115 participants, values for medications were missing. Participants with significant valvular heart disease and missing or invalid results on echocardiography were excluded.

‡ $P = 0.035$ for comparisons among study subgroups.

§ $P = 0.001$ for comparisons among study subgroups.

‖ $P > 0.2$ for comparisons among study subgroups.

¶ Frequent aspirin use was defined as a prescription for aspirin or >7 days of use in the previous 2 weeks.

six groups were identified by congestive heart failure status and left ventricular systolic function at baseline: 1) no congestive heart failure and normal left ventricular systolic function, 2) no congestive heart failure and borderline systolic function, 3) no congestive heart failure and impaired systolic function, 4) congestive heart failure and normal systolic function, 5) congestive heart failure and borderline systolic function, and 6) congestive heart failure and impaired systolic function.

Statistical Analysis

Chi-square tests or analysis of variance was used for unadjusted analyses of the associations among groups and baseline variables. Age- and sex-adjusted associations were investigated by using logistic regression models or analysis of covariance, using the six subgroups as predictors (32).

Event rates per 1000 person-years at risk are presented for each type of incident event. Cox proportional hazard regression techniques were used to examine the association of the six subgroups with time to incident events after adjustment for covariates (33). Covariates included factors previously associated with poor outcome in other population-based investigations of survival, as well as baseline variables significantly associated with incident events in our study. These included age, sex, black ethnicity, weight, systolic blood pressure, diastolic blood pressure, diabetes, history of coronary heart disease, FEV$_1$, ankle–arm index dichotomized at 0.9, atrial fibrillation on electrocardiography, intima–media thickness for common and internal carotids, creatinine concentration, cholesterol level, alcoholic drinks per week, left ventricular mass, early and late mitral inflow velocity on Doppler ultrasonography, left atrial dimension, mitral regurgitation, medications (β-blockers, angiotensin-converting enzyme inhibitors, lipid-lowering drugs, diuretics, calcium-channel blockers, aspirin, digitalis), and clinic. In addition, we included a term to adjust for clustering within clinic, using the cluster(clinic) option of the coxph function in S-Plus 2000 (Insightful Corp., Seattle, Washington).

The variables for mitral regurgitation, cholesterol level, and lipid-lowering medications were highly nonsignificant and did not behave as confounders for group in any of the models. That is, once these variables were removed from the model, estimates of hazard ratios for levels of the group variable changed at most in the second decimal place. In addition, removal of these variables improved the results of the overall tests of the proportional hazards assumption so that all models satisfied a *P* value greater than or equal to 0.08. For these reasons, mitral regurgitation, cholesterol level, and lipid-lowering medications were omitted from all adjusted models.

A statistic (mortality impact, also known as population attributable risk) was calculated to express the impact of the clinical condition (congestive heart failure with normal, borderline, or impaired systolic function) on the expected population mortality rate, based on the mortality risk and the prevalence of the condition in our population-based cohort (32). All statistical analyses were conducted by using S-Plus 2000, release 3.

Role of the Funding Source

This study was funded through contracts with the National Heart, Lung, and Blood Institute (NHLBI) and included substantial NHLBI involvement in data collection, analysis, and interpretation and manuscript preparation.

RESULTS

Prevalence of Congestive Heart Failure and Left Ventricular Function

Congestive heart failure was identified in 300 of 5888 participants (5.1%), and left ventricular systolic function was assessable in 5649 participants (96%). Of the 5532 participants remaining after those with significant valvular heart disease were excluded, 269 (4.9%) had congestive heart failure; 52% of these were women. Baseline left ventricular function was normal in 170 participants with congestive heart failure (63%), borderline in 39 (15%), and impaired in 60 (22%).

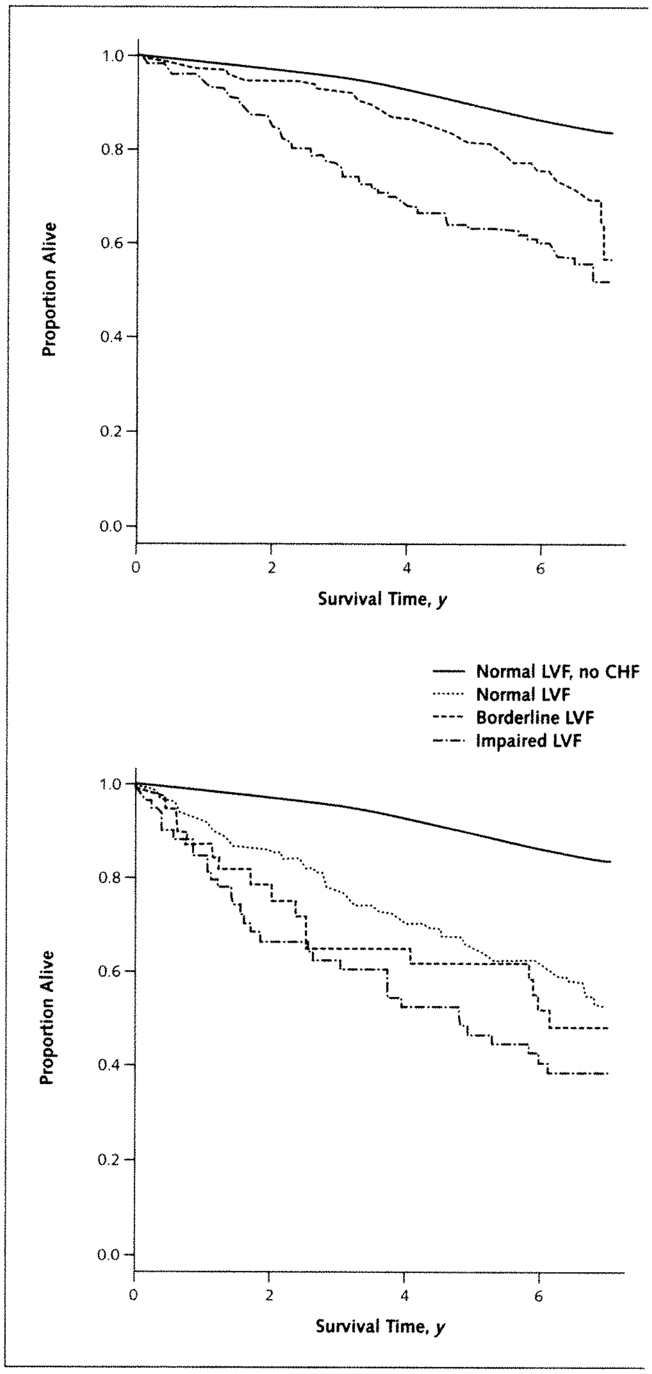
Baseline Characteristics of Study Groups

Comparison of baseline characteristics among groups is shown in **Table 1**. Compared with the other groups, the group with congestive heart failure and impaired left ventricular systolic function had lower mean systolic blood pressure, included more participants with clinically evident coronary artery disease and subclinical atherosclerosis (increased intima–media thickness of the internal carotid artery, low ankle–arm index), had higher serum creatinine concentrations, and had greater left ventricular mass. When we compared participants who had congestive heart failure and normal left ventricular function with those who had impaired function, the former group was older, had higher mean systolic blood pressure, included more women, included fewer persons with clinically evident coronary artery disease, had lower serum creatinine concentrations, and had lower left ventricular mass. Use of cardiovascular medications at baseline is shown in **Table 2**. Statistically significant differences were seen among study groups for all cardiac medications, with the exception of lipid-lowering drugs.

Unadjusted All-Cause Mortality

The mortality rate was 25 deaths per 1000 person-years in the reference group (no congestive heart failure and normal left ventricular function at baseline); 154 deaths per 1000 person-years in participants with congestive heart failure and impaired left ventricular systolic function; 87 and 115 deaths per 1000 person-years in participants with congestive heart failure and normal or borderline systolic function, respectively; and 89 deaths per 1000 person-years in persons with impaired left ventricular function but no congestive heart failure. Participants without congestive heart failure had a higher mortality rate with impaired ($P < 0.001$) and borderline ($P < 0.001$) left ventricular systolic function when compared with the reference group (no congestive heart failure and normal systolic function) (**Figure**).

Figure. **Unadjusted Kaplan–Meier survival curves for participants with no congestive heart failure (*CHF*) (*top*) and for those with CHF (*bottom*) based on left ventricular function (*LVF*).**



In participants with congestive heart failure, the all-cause mortality rate was 45% at a median follow-up of 6.4 years compared with 16% in those without congestive heart failure ($P < 0.001$). Participants with congestive heart failure and normal left ventricular function had a

Table 3. **Event Rates and Hazard Ratios***

Study Group	Nonfatal Myocardial Infarction			Stroke		
	Event Rate	Unadjusted Hazard Ratio in 383 Participants	Adjusted Hazard Ratio in 331 Participants	Event Rate	Unadjusted Hazard Ratio in 424 Participants	Adjusted Hazard Ratio in 340 Participants
No CHF, normal LV systolic function	10.9	1.0	1.0	12.5	1.0	1.0
No CHF, borderline LV systolic function	29.7	2.74 (2.0–3.8)	2.00 (1.4–2.8)	21.4	1.73 (1.2–2.5)	1.26 (0.9–1.7)
No CHF, impaired LV systolic function	36.8	3.39 (2.2–5.2)	1.42 (0.9–2.2)	33.0	2.67 (1.7–4.2)	1.27 (1.0–1.6)
CHF, normal LV systolic function	23.3	2.16 (1.3–3.5)	1.44 (0.6–3.4)	27.5	2.23 (1.4–3.5)	1.27 (0.9–1.8)
CHF, borderline LV systolic function	37.7	3.52 (1.5–8.5)	2.17 (1.2–4.0)	50.7	4.15 (2.0–8.8)	2.41 (1.3–4.5)
CHF, impaired LV systolic function	19.4	1.81 (0.7–4.9)	0.92 (0.4–2.1)	45.2	3.69 (1.9–7.2)	1.91 (1.3–2.7)

* Values in parentheses are 95% CIs. All hazard ratios are based on Cox proportional hazards models. Event rates are expressed as rates per 1000 person-years at risk. Adjusted models include the following terms: age, sex, African-American ethnicity, weight, systolic blood pressure, diastolic blood pressure, diabetes, history of coronary heart disease, FEV_1, ankle–arm index dichotomized at 0.9, atrial fibrillation on electrocardiography, intima–media thickness for common and internal carotids, creatinine concentration, alcoholic drinks per week, LV mass, early and late mitral inflow velocity on Doppler ultrasonography, left atrial dimension, β-blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium-channel blockers, digitalis, frequent aspirin use, clinic site, and a term to adjust for clustering within clinic. CHF = congestive heart failure; LV = left ventricular.

mortality rate that was significantly higher than that in the reference group ($P < 0.001$) (**Figure**) and was similar to that in participants with impaired function but no congestive heart failure. Impaired (but not borderline) left ventricular function was associated with higher mortality rates among participants with congestive heart failure ($P = 0.007$).

Adjusted All-Cause and Cardiovascular Mortality

After adjustment for covariates, the risk for all-cause mortality was significantly increased in persons with congestive heart failure and normal, borderline, or impaired left ventricular systolic function compared with the reference group (**Table 3**). The risk for all-cause mortality was also greater in participants with no congestive heart failure who had impaired or borderline left ventricular function.

The adjusted risk for cardiovascular mortality was increased in persons with borderline or impaired left ventricular function but no congestive heart failure and in persons with congestive heart failure and impaired left ventricular function. The risk was not significantly increased in persons with congestive heart failure and borderline left ventricular function (adjusted hazard ratio, 2.39 [95% CI, 0.9 to 6.1]) or congestive heart failure and normal left ventricular function (adjusted hazard ratio, 1.29 [CI, 0.9 to 1.9]).

Risk for Nonfatal Myocardial Infarction and Stroke

Compared with the reference group, all groups except the group with congestive heart failure and impaired left ventricular function were at increased risk for nonfatal myocardial infarction and stroke (**Table 3**). Participants with borderline left ventricular function with or without heart failure remained at risk for nonfatal myocardial infarction after adjustment for covariates, whereas participants in the other groups did not. Risk for stroke remained increased only in persons with congestive heart failure and borderline or impaired left ventricular function and was of borderline significance in those with impaired function but no heart failure.

Mortality Impact of Heart Failure with Normal versus Impaired Systolic Function

The mortality impact (population attributable risk) from any cause was greatest (7.5%) in the group with congestive heart failure and normal left ventricular function, reflecting the combined effect of moderate risk and high prevalence of heart failure in the presence of normal systolic function. In contrast, the mortality impact of congestive heart failure in participants with impaired systolic function was 5.9% despite the higher hazard ratio. This finding was due to the lower prevalence of impaired systolic function in persons with heart failure.

DISCUSSION

Previous reports from the Cardiovascular Health Study have demonstrated that most community-based elderly persons with congestive heart failure have normal left ventricular systolic function (34); that normal systolic function most commonly precedes incident congestive heart failure (35); and that the predictors of congestive heart failure in elderly persons (35, 36) with or without systolic dysfunction include clinical and subclinical coronary heart disease, systolic blood pressure, inflammation, left atrial size, and diastolic dysfunction. Our principal finding is that community-based elderly persons with congestive heart failure have a substantial risk for death, even in the presence of normal or borderline decreased left ventricular systolic function. Although the adjusted mortality risk was greatest in participants with congestive heart failure and abnormal left ventricular systolic function, only a minority of community-based elderly persons were in this category. Therefore, the mortality impact of death from any cause after a diagnosis of congestive heart failure was greater in persons with normal left ventricular systolic function than in those with borderline or impaired function. Since we excluded participants with clinically significant valvular heart disease, our findings probably represent the adverse outcome of what has commonly been termed

Table 3—**Continued**

Cardiovascular Mortality			All-Cause Mortality		
Event Rate	**Unadjusted Hazard Ratio in 397 Participants**	**Adjusted Hazard Ratio in 317 Participants**	**Event Rate**	**Unadjusted Hazard Ratio in 952 Participants**	**Adjusted Hazard Ratio in 759 Participants**
9.0	1.0	1.0	25.1	1.0	1.0
33.3	3.71 (2.7–5.0)	2.08 (1.7–2.6)	51.0	2.05 (1.6–2.6)	1.25 (1.1–1.4)
50.5	5.80 (4.0–8.3)	2.13 (1.7–2.7)	88.7	3.69 (2.8–4.8)	1.83 (1.2–2.7)
40.9	4.72 (3.3–6.8)	1.29 (0.9–1.9)	87.0	3.62 (2.8–4.6)	1.48 (1.2–1.8)
67.9	8.03 (4.3–15.1)	2.39 (0.9–6.1)	115.4	4.94 (3.1–8.0)	2.40 (1.2–4.6)
98.1	11.74 (7.5–18.3)	2.14 (1.5–3.1)	154.1	6.70 (4.7–9.5)	1.88 (1.0–3.4)

isolated diastolic heart failure (37). However, we recognize that without measures of diastolic function, this is a diagnosis of exclusion. Of particular interest in our study was the finding that the adjusted risk for all-cause and cardiovascular death was similar in participants with no clinical congestive heart failure but impaired systolic function and participants with congestive heart failure and impaired function, although the former group included more than twice as many persons as the latter. The 6-year mortality rate of 45% in participants reporting congestive heart failure was somewhat lower than the rate of 60% to 75% reported in other epidemiologic studies (1, 15, 22) but was highly statistically significant compared with persons without congestive heart failure, in whom the 6-year mortality rate was 16%.

Although left ventricular systolic performance has been established as an important predictor of outcome in persons with acute myocardial infarction (38, 39) and those with symptomatic ventricular arrhythmias (40, 41), studies differ about the impact of systolic function on prognosis after congestive heart failure is diagnosed (17, 22, 23, 39, 42–44). We extended previous findings (22, 23) by evaluating a community-based sample made up exclusively of elderly persons and determining that congestive heart failure in elderly persons is associated with poor prognosis with or without impaired left ventricular systolic function. In contrast to the findings of the Olmstead County study (22) and the recent study published by the Italian Network on Congestive Heart Failure Investigators (44), we found that impaired systolic function was associated with greater risk for death than normal systolic function after a diagnosis of congestive heart failure. Although data from previous studies are conflicting (1, 15), we also found that this association was independent of male sex. Another finding of our study, not previously underscored in the literature, was the observation that the mortality impact of congestive heart failure was greater in elderly persons with normal left ventricular systolic function than in those with impaired systolic function, reflecting the lower prevalence of impaired systolic function.

It is of interest that the relationship between borderline left ventricular function and increased risk for nonfatal myocardial infarction persisted in adjusted models. This suggests that a mild and clinically inapparent decrease in left ventricular function nonetheless indicates increased risk for myocardial infarction, even after other markers of atherosclerosis severity are taken into account.

The six groups in our study were based in part on a qualitative assessment of global left ventricular systolic function. However, this assessment was performed in a centralized, experienced core laboratory with multiple quality controls. The articulation and accurate application of an appropriate definition of the clinical syndrome of congestive heart failure have been problematic in clinical studies. Since this was an epidemiologic study, we cannot definitively exclude the possibility that some participants classified as having congestive heart failure may have had dyspnea from noncardiac causes. To minimize such a possibility, some previous studies have required the presence of substantial decreases in left ventricular systolic ejection fraction for diagnosis. However, as our findings suggest, this would create a tautology by which it would not be possible to identify congestive heart failure in the absence of systolic dysfunction. It has been shown that acute pulmonary edema can occur in the presence of normal systolic function (45, 46) and that left atrial pressure is increased at rest and during exercise in patients with congestive heart failure and normal systolic function, as occurs in affected patients with impaired systolic function (9). Also, since many persons in this and other studies (45) have decreased systolic function without congestive heart failure, the finding of decreased systolic function may not always be helpful in determining whether dyspnea or suspicious roentgenographic findings are of cardiac origin.

The term *diastolic heart failure* has been used to describe congestive heart failure with normal left ventricular systolic function in the absence of valvular disease caused by physiologic characteristics of heart failure. Criteria have recently been proposed for this entity (37), including determination of normal ventricular systolic function within

72 hours of the sentinel event of clinical heart failure (that is, "probable" diastolic heart failure) and invasive measurement of abnormal myocardial relaxation (that is, "definite" diastolic heart failure). Invasive measurement of myocardial relaxation was not possible in our epidemiologic study and may not be relevant to clinical practice. We did not use other scoring systems or criterion-based algorithms for diagnosis of congestive heart failure.

In our study, ventricular systolic function was determined at a baseline examination variably remote from the sentinel clinical event of congestive heart failure. It has been shown, however, that systolic function may remain relatively stable after the onset of clinical findings of heart failure (46). We found that more participants had congestive heart failure and normal left ventricular systolic function than has previously been reported (5). This may be due to survival effects, whereby persons with particularly poor systolic function would be more likely to die or be otherwise unavailable for evaluation. It is also possible that systolic function may have improved between the onset of congestive heart failure and the time of the study echocardiography, although previous reports suggest that this is uncommon (7, 46). Notably, tabulation of clinical echocardiography reports retrieved from 145 of 170 cases of incident congestive heart failure in the Cardiovascular Health Study showed that 57% of persons had normal left ventricular systolic function at the time of hospitalization for congestive heart failure (36). Also, the presumably better health of our noninstitutionalized sample compared with other study samples (22, 23) may have resulted in selection of more participants with congestive heart failure and normal systolic function.

Up to 88% of congestive heart failure cases (3, 22) and 90% of deaths from congestive heart failure (48) occur in elderly persons. Despite this, however, most epidemiologic studies of heart failure and treatment trials on which current principles of heart failure pharmacotherapy are based have addressed a predominantly male population younger than 65 years of age with substantially impaired left ventricular systolic function (49–54). Such studies generally require a ventricular ejection fraction of less than 0.45, or even less than 0.35, as a criterion for enrollment. Therefore, the results of such clinical trials may not be applicable to elderly persons and others with congestive heart failure and preserved left ventricular function.

Elderly persons have a substantial risk for death after a diagnosis of congestive heart failure, and normal left ventricular systolic function does not ensure favorable outcome. Given the large proportion of elderly persons in the population, the greatest opportunity for reducing death from heart failure may lie in the successful treatment of those with normal left ventricular systolic function.

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Short-Course Rifampin and Pyrazinamide Compared with Isoniazid for Latent Tuberculosis Infection: A Multicenter Clinical Trial

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Background: **Rifampin and pyrazinamide are recommended for treatment of latent tuberculosis infection in adults without HIV infection, but reports of severe hepatotoxicity have raised concerns about its safety. Clinical trials have not compared this treatment with isoniazid in adults without HIV infection.**

Objective: **To compare the safety and tolerance of a 2-month regimen of rifampin and pyrazinamide with that of a 6-month regimen of isoniazid for treatment of latent tuberculosis infection.**

Design: **Multicenter, prospective, open-label trial.**

Setting: **Three urban public health tuberculosis clinics in the United States.**

Patients: **589 adults with latent tuberculosis infection who met U.S. criteria for treatment.**

Intervention: **Patients were assigned in alternate weeks to receive rifampin and pyrazinamide daily for 2 months (n = 307) or isoniazid daily for 6 months (n = 282).**

Measurements: **Primary end points were hepatotoxicity, other adverse events, and percentage of patients who completed treatment.**

Results: **Sixteen of 207 (7.7%) patients assigned to rifampin and pyrazinamide developed grade 3 or 4 hepatotoxicity compared with 2 of 204 (1%) patients assigned to isoniazid (odds ratio, 8.46 [95% CI, 1.9 to 76.5]; P = 0.001). The rifampin plus pyrazinamide regimen was more likely than the isoniazid regimen to be discontinued because of hepatotoxicity (odds ratio, 5.19; P = 0.033). The overall percentage of nonhepatotoxic adverse events was 20% in the rifampin–pyrazinamide group and 16% in the isoniazid group. The proportion of patients who completed the study treatment was 61% and 57%, respectively.**

Conclusions: **A 2-month regimen of rifampin and pyrazinamide was associated with an increased risk for grade 3 or 4 hepatotoxicity compared with a 6-month regimen of isoniazid. Liver enzymes should be measured routinely during treatment to screen for liver injury and prevent progression to severe toxicity.**

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See editorial comment on pp 693-695.

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As rates of tuberculosis cases in the United States have decreased (1, 2), the focus of prevention and control efforts has shifted toward identification and treatment of persons with latent tuberculosis infection who are at increased risk for developing tuberculosis. This approach was endorsed in a recent report from the Institute of Medicine (3).

Isoniazid given for at least 6 months has been the standard therapy for latent tuberculosis infection for decades, but its use has been limited by toxicity, especially hepatitis (4–6), and by poor adherence to treatment (7). A 2-month course of rifampin and pyrazinamide has been shown to be effective and well tolerated as treatment of latent tuberculosis infection in HIV-infected persons (8–10). Guidelines from the American Thoracic Society and Centers for Disease Control and Prevention (11) offer three main regimens for treatment of latent tuberculosis infection: isoniazid for 6 to 9 months, rifampin for 4 months, or rifampin and pyrazinamide for 2 months. However, there is relatively little experience with use of rifampin plus pyrazinamide to treat latent tuberculosis infection in persons without HIV infection, and case reports of severe hepatitis causing five deaths have raised concerns about the safety of the regimen (12, 13).

We therefore conducted a multicenter, prospective, open-label trial comparing daily treatment with rifampin and pyrazinamide for 2 months with daily treatment with isoniazid for 6 months in non–HIV-infected adults with latent tuberculosis infection (the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection [SCRIPT] study). Our primary goals were to compare risk for toxicity, particularly hepatotoxicity, and completion of therapy. We also investigated whether persons with latent tuberculosis infection who were older than 35 years of age, a group known to have increased rates of hepatitis while taking isoniazid (5), would have fewer adverse events while taking rifampin plus pyrazinamide than while taking isoniazid.

METHODS

Patients

All adults older than 17 years of age who had a positive tuberculin skin test (as defined by American Thoracic Society/Centers for Disease Control and Prevention criteria [11]) and in whom active tuberculosis was excluded and treatment of latent tuberculosis infection would ordinarily be recommended (for example, persons with close contact to an infectious case or those with a medical risk factor, such as diabetes) were eligible for the study. In addition, we enrolled foreign-born persons older than 35 years of age who had been in the United States for fewer than 6 years. These latter patients were not included in the American

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Thoracic Society/Centers for Disease Control and Prevention guidelines when the study was begun.

Before being invited to participate, all patients who met initial criteria for enrollment were asked about previous liver disease, current medications and illnesses, previous gout, and risk factors for HIV infection. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase, and alkaline phosphatase), bilirubin, and creatinine were measured. Testing for and counseling about HIV infection were recommended for patients whose HIV status was not known, and a urine pregnancy test was performed for all women of childbearing age. During their baseline visit, patients underwent a review of symptoms that included history of nausea, vomiting, jaundice, abdominal pain, weight loss, arthralgia, headache, and neuropathy.

Exclusion criteria were pregnancy, HIV infection, serum creatinine concentration more than twice the upper limit of normal, serum aspartate aminotransferase or ALT level more than three times the upper limit of normal, and a history of gout. Institutional review boards at each site approved the study, and written informed consent was obtained from all patients.

Design

Persons who met study criteria and agreed to participate were allocated in alternate weeks to receive rifampin (600 mg/d) plus pyrazinamide (20 mg/kg of body weight daily) for 2 months or isoniazid (300 mg/d) for 6 months (the recommended minimum duration when the study started [14]). Tables were used to standardize weight-based dosing of pyrazinamide to the closest 250 mg. At each site, the allocation during the first week of patient enrollment was determined by a coin toss. For the remainder of the trial, allocation to treatment regimen was alternated weekly. This systematic allocation design was chosen for ease of implementation in busy public health tuberculosis clinics in San Francisco, Boston, and Atlanta.

Serum levels of liver enzymes and bilirubin were measured in all patients after 1 month of treatment. Patients receiving isoniazid had repeated liver enzyme testing at 3 months. Patients receiving rifampin and pyrazinamide also had a complete blood count and measurement of uric acid and creatinine after 1 month of treatment.

All treatment was self-administered, and specific incentives, financial or otherwise, were not provided. All patients received monthly supplies of medication and were instructed to take medication daily and return in 1 month (or sooner if any of the symptoms mentioned previously occurred). At each visit, patients were evaluated for signs and symptoms of adverse events by tuberculosis control nurses and evaluated for adherence to treatment.

Hepatotoxicity was based on the World Health Organization classification and was defined as grade 1 for any serum ALT level of 51 to 125 U/L, or 1.25 to 2.5 times normal; grade 2 for any serum ALT level of 126 to 250 U/L, or 2.6 to 5.0 times normal; grade 3 for any serum ALT level of 251 to 500 U/L, or 5.1 to 10.0 times normal; and grade 4 for any serum ALT level greater than 500 U/L, or >10 times normal, or greater than 250 U/L if accompanied by compatible symptoms (15).

Context

Guidelines from the American Thoracic Society and Centers for Disease Control and Prevention for treating latent tuberculosis infection advocate 2 months of rifampin plus pyrazinamide as an effective alternative to 6 to 9 months of isoniazid or 4 months of rifampin. However, case reports have described severe liver injury in patients who were receiving the 2-month regimen.

Contribution

This nonrandomized, open-label trial found that the risk for grade 3 or 4 liver injury was higher in patients taking 2 months of rifampin plus pyrazinamide (7.7%) than in patients taking 6 months of isoniazid (1%).

Clinical Implications

If clinicians use the short-course regimen, they should vigilantly follow patients' liver enzyme levels.

–The Editors

At the 1-month evaluation in recipients of rifampin plus pyrazinamide or the 3-month evaluation in isoniazid recipients, patients who had grade 1 or 2 liver injury continued to take study medication and had repeated liver enzyme testing in 2 weeks. In patients with grade 3 hepatotoxicity, treatment with study drugs was stopped and not resumed unless another cause of hepatitis could be found (such as alcohol abuse). Treatment with study drugs was permanently discontinued in patients with grade 4 hepatotoxicity.

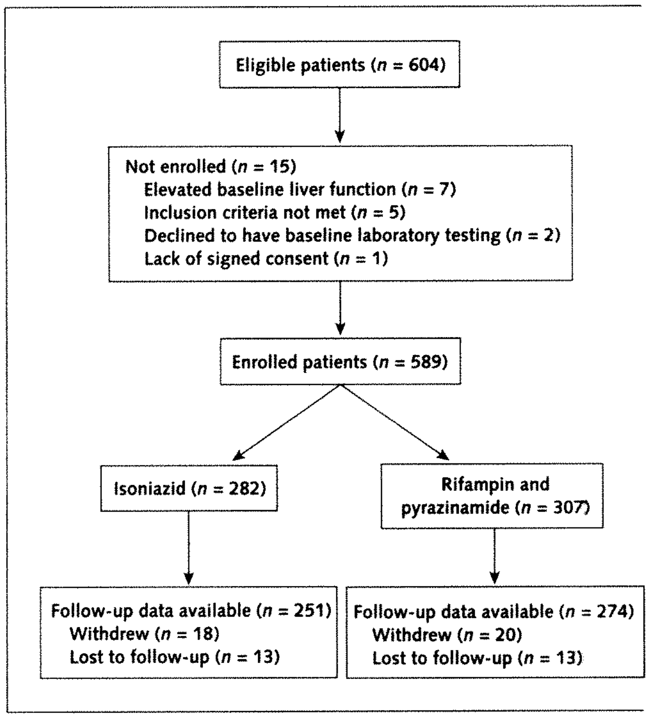
Outcomes

Primary end points were development of any adverse event, especially grade 3 or 4 hepatotoxicity, and completion of the prescribed amount of treatment. Adverse events were determined on the basis of interviews and by laboratory examination when indicated. Completion of the regimen was defined as taking at least 80% of prescribed medication.

Statistical Analysis

A sample of 540 patients was calculated to provide 80% power in two-sided tests, with an α value of 0.05, to detect an increase in the expected incidence of hepatotoxicity of any grade (the primary end point) from 15% in the isoniazid group to 25% in the rifampin plus pyrazinamide group. The first patient was enrolled on 15 February 1999. A scheduled interim analysis of the first 313 patients that was performed in July 2000 indicated no statistically significant differences between the two groups in terms of adverse events or completion of therapy. Enrollment continued until October 2000.

Figure 1. **Flow of patients through the study.**


Eligible patients (n = 604)
Not enrolled (n = 15)
Elevated baseline liver function (n = 7)
Inclusion criteria not met (n = 5)
Declined to have baseline laboratory testing (n = 2)
Lack of signed consent (n = 1)
Enrolled patients (n = 589)
Isoniazid (n = 282)
Rifampin and pyrazinamide (n = 307)
Follow-up data available (n = 251)
Withdrew (n = 18)
Lost to follow-up (n = 13)
Follow-up data available (n = 274)
Withdrew (n = 20)
Lost to follow-up (n = 13)

Fifteen of 604 patients were excluded. The proportion of patients for whom follow-up data were available was similar in the isoniazid group and the rifampin plus pyrazinamide group (89.0% vs. 89.2%, respectively).

Between-regimen comparisons of hepatotoxicity, other adverse events, and completion were based on the treatment initially assigned, without regard to the duration of treatment actually received. In an initial analysis of treatment effects on hepatotoxicity, the Fisher exact test was used to compare the proportion of patients with ALT values greater than 250 U/L among 411 participants who had liver enzyme testing at 1 or 3 months. Confirmatory analyses were then used to validate the initial result. Because the study was not randomized, treatment assignment was potentially confounded by imbalances in baseline covariates between the two treatment groups. In addition, grade 3 or 4 hepatotoxicity was uncommon. Therefore, to adjust for potential confounding, the initial exact analysis of hepatotoxicity was repeated with stratification by quintile of a propensity score that was estimated by using a multivariable logistic model for treatment assignment (16, 17). Furthermore, liver enzyme values were missing for 78 of 282 (27.7%) patients in the isoniazid group and 100 of 307 (32.6%) patients in the rifampin plus pyrazinamide group. To correct for this possible source of bias, we used multiple imputation. Specifically, the odds ratio for treatment was estimated in each of 10 data sets with imputed values for the missing liver enzyme tests by using logistic models to adjust for the propensity score as a continuous covariate. In the final step, a summary odds ratio estimate was calculated by using standard methods (18, 19).

In a further analysis, treatment-by-site interaction was examined in an exact analysis that was stratified by site. We also used logistic models to assess possible violations of independence due to clustering by site by comparing model-based standard errors with robust standard errors that accounted for within-site correlation. Finally, more common outcomes, including completion of treatment regimen and nonhepatotoxic adverse events, were analyzed by using the Fisher exact test. Analyses were done by using SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina), and StatXact software, version 4 (Cytel Software Corp., Cambridge, Massachusetts).

Role of the Funding Source

The funding source had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

RESULTS

Clinical and Demographic Characteristics at Baseline

Five hundred eighty-nine patients were enrolled from the three clinical sites (**Figure 1**). A high proportion of the patients were born outside the United States, the criterion that constituted the indication for treatment in 65.5% (**Table 1**). The two groups were similar in sex and body weight. A higher proportion of isoniazid recipients were older than 35 years of age and were born outside the United States.

Hepatotoxicity

Among patients who had follow-up liver enzyme tests, hepatotoxicity developed in 54 of 207 (26%) recipients of the rifampin–pyrazinamide regimen (of whom 16 had grade 3 or 4 hepatotoxicity) compared with 32 of 204 (16%) isoniazid recipients (2 of whom had grade 3 or 4 hepatotoxicity) (**Table 2**). Among patients with liver enzyme test results at 1 month, 1 of 199 (0.5%) isoniazid

Table 1. **Baseline Characteristics of 589 Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid To Treat Latent Tuberculosis Infection**

Variable	Rifampin and Pyrazinamide Group (*n* = 307)	Isoniazid Group (*n* = 282)
Age > 35 y, *n (%)*	99 (32)	114 (40)
Men, *n (%)*	174 (57)	154 (55)
Mean body weight ± SD, *kg*	71.4 ± 15.3	70.5 ± 15.3
Born outside the United States, *n (%)*	253 (83)	249 (88)
Asia or Pacific Islands	114	113
Latin/South America	55	51
Africa	38	43
Europe	33	24
Caribbean islands	12	18
Indication for treatment, *n*		
New arrival to the United States	197	189
Contact with infectious case	49	48
Tuberculin converter	38	28
Health care worker	18	11
Medical risk factor	5	6

Table 2. **Hepatotoxicity in 411 Patients for Whom Follow-up Liver Enzyme Test Results Were Available***

Hepatotoxicity†	Rifampin and Pyrazinamide Group (*n* = 207)	Isoniazid Group (*n* = 204)
	n (%)	
Grade 1	29 (14)	27 (13.2)
Grade 2	9 (4.3)	3 (1.5)
Grade 3	7 (3.4)	0 (0)
Grade 4	9 (4.3)	2 (1.0)
Total	54 (26.1)	32 (15.7)
Discontinuation of study medications owing to hepatotoxicity	12 (5.8)	2 (1.0)

* The unit of analysis is the patient.

† Grade 1 hepatotoxicity was defined as a serum alanine aminotransferase (ALT) level of 51 to 125 U/L, or 1.25 to 2.5 times normal; grade 2 as serum ALT level 126 to 250 U/L, or 2.6 to 5.0 times normal; grade 3 as serum ALT level 251 to 500 U/L, or 5.1 to 10.0 times normal; and grade 4 as serum ALT level >500 U/L, or >10 times normal, or >250 U/L if accompanied by compatible symptoms. Criteria are based on those in reference 15.

recipients and 16 of 207 (7.7%) recipients of rifampin plus pyrazinamide had ALT levels of 250 U/L or greater, consistent with grade 3 or 4 hepatotoxicity (odds ratio, 16.6 [95% CI, 2.52 to 699]; $P < 0.001$). Among patients who had liver enzyme testing at 1 or 3 months, the proportion with ALT levels of 250 U/L or greater on at least one test increased to 2 of 204 (1%) patients in the isoniazid group. In the rifampin plus pyrazinamide group, liver enzymes were measured at 1 month only (odds ratio, 8.46 [CI, 1.94 to 76.5]; $P = 0.001$). No patient had more than one episode of hepatotoxicity.

Treatment with rifampin and pyrazinamide was more likely than treatment with isoniazid to be discontinued because of hepatotoxicity (odds ratio, 5.19 [CI, 1.11 to 49.1]; $P = 0.033$). No patient in either group was hospitalized for hepatitis, and all patients had resolution of hepatic abnormalities after discontinuation of therapy with medications. The maximum ALT concentrations of patients with grade 4 hepatotoxicity ranged from 695 to 1187 U/L. Approximately 70% of isoniazid-associated hepatotoxicity of any grade was discovered by liver enzyme testing after the first month of treatment, and both cases of grade 4 hepatotoxicity in patients receiving isoniazid occurred during the first 2 months of treatment. No patient who developed grade 3 or 4 hepatotoxicity had evidence of active hepatitis B or C viral infection.

Confirmatory Analyses

In the confirmatory exact analysis that was stratified by quintile of the propensity score, therapy with rifampin plus pyrazinamide was strongly associated with increased risk for grade 3 or 4 hepatotoxicity (odds ratio, 7.75 [CI, 1.74 to 71.3]; $P = 0.003$) and any hepatotoxicity (odds ratio, 1.77 [CI, 1.04 to 3.04]; $P = 0.033$) compared with isoniazid therapy (Table 3). The multiple imputation estimates were consistent with the exact results for both grade 3 or 4 hepatotoxicity (odds ratio, 8.57 [CI, 1.93 to 38.0]; $P = 0.005$) and any hepatotoxicity (odds ratio, 1.53 [CI, 0.95 to 2.47]; $P = 0.08$) (Table 3). There was little evidence of heterogeneity of the treatment effect on any grade of hepatotoxicity ($P > 0.2$) and no evidence of clustering by site.

Nonhepatotoxic Adverse Events

The overall occurrence of adverse events not due to hepatotoxicity was similar in the treatment groups (20% among recipients of rifampin and pyrazinamide and 16% among isoniazid recipients [$P = 0.2$]) (Table 4). Skin rash was the only nonhepatotoxic adverse effect that occurred more frequently with rifampin plus pyrazinamide (6%) than with isoniazid (2%) ($P = 0.01$). The occurrence of other adverse events did not significantly differ between groups. However, discontinuation of medication use because of nonhepatotoxic adverse events was more common among patients who received rifampin and pyrazinamide than those who received isoniazid ($P = 0.049$). Results were similar among the 525 patients with postenrollment follow-up. Univariate analysis of predictors of nonhepatotoxic adverse events in recipients of rifampin and pyrazinamide for whom follow-up data were available were female sex (odds ratio, 2.35 [CI, 1.33 to 4.15]; $P = 0.003$) and a trend toward recent arrival in the United States (odds ratio, 1.68 [CI, 0.95 to 2.96]; $P = 0.07$). Univariate predictors

Table 3. **Odds Ratios for Incidence of Grade 3 or 4 Hepatotoxicity in Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid**

Method of Analysis	Treatment Group	Patients, *n*	Odds Ratio (95% CI)	*P* Value
Observed data	Rifampin and pyrazinamide	207	8.46 (1.9–76.5)	0.001
	Isoniazid	204	Referent	–
Stratified exact*	Rifampin and pyrazinamide	207	7.75 (1.74–71.3)	0.003
	Isoniazid	204	Referent	–
Multiple imputation†	Rifampin and pyrazinamide	307	8.57 (1.93–38.0)	0.005
	Isoniazid	282	Referent	–

* The exact odds ratio, CI, and *P* value are derived from the noncentral hypergeometric distribution of tabulations of grade 3 and 4 hepatotoxicity by treatment assignment, stratified by quintile of the propensity score and conditional on the number of cases of hepatotoxicity in each stratum. Propensity scores were estimated by using a multivariable logistic model that included site, sex, age >35 years, baseline body weight, tuberculin conversion, presence of related medical conditions, and being a health care worker, as well as interactions between site and baseline body weight, sex, and being a health care worker.

† Missing alanine aminotransferase values were simulated in 10 data sets by using SAS Proc IM separately for each arm of the trial. The imputation model for the isoniazid arm included site, sex, age >35 years, baseline weight, birth in the United States, and nonmissing liver enzyme values. The model for the rifampin plus pyrazinamide arm included these covariates plus an indicator for health care workers. Imputed alanine aminotransferase values ≥251 U/L were then classified as grade 3 or 4 hepatotoxicity. One to four cases of hepatotoxicity were imputed among recipients of rifampin and pyrazinamide; no cases were imputed among isoniazid recipients.

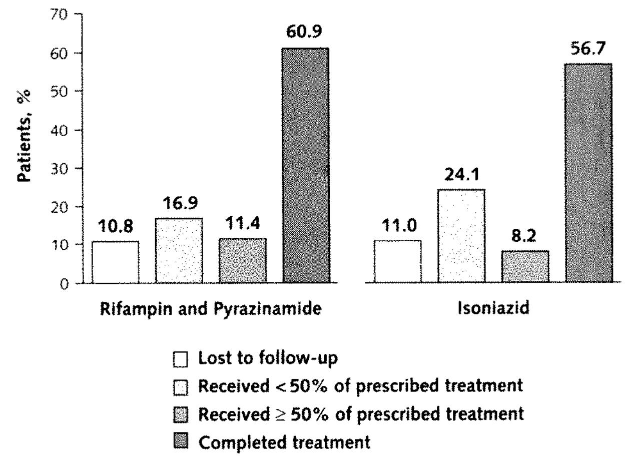
Table 4. **Nonhepatotoxic Adverse Events in the 589 Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid To Treat Latent Tuberculosis Infection**

Adverse Effect	Rifampin and Pyrazinamide Group (*n* = 307)	Isoniazid Group (*n* = 282)	*P* Value*
	n (%)		
At least 1 adverse effect	62 (20)	46 (16)	0.2
Nausea or vomiting	18 (6)	12 (4)	>0.2
Skin rash	19 (6)	5 (2)	0.007
Epigastric pain	9 (3)	8 (3)	>0.2
Fatigue or malaise	11 (4)	14 (5)	>0.2
Dizziness	3 (1)	5 (2)	>0.2
Headache	5 (2)	4 (1)	>0.2
Fever or chills	1 (0.3)	1 (0.4)	>0.2
Arthralgia	1 (0.3)	5 (2)	0.11
Diarrhea	3 (1)	2 (1)	>0.2
Peripheral neuropathy	0 (0)	1 (0.4)	>0.2
Anorexia/weight loss	3 (1)	1 (0.4)	>0.2
Insomnia	0 (0)	2 (1)	0.2
Pruritus	3 (1)	1 (0.4)	>0.2
Dysmenorrhea	1 (1)	0 (0)	>0.2
Discontinuation of study medication owing to nonhepatotoxic adverse effect	16 (5)	6 (2)	0.053

* Between-treatment differences were assessed by using the Fisher exact test. Results were similar when analysis was restricted to the 525 participants who were not lost to follow-up after the start of the trial.

of nonhepatotoxic adverse events in isoniazid recipients for whom follow-up data were available included age older than 35 years (odds ratio, 1.96 [CI, 1.06 to 3.62]; *P* = 0.03) and birth in the United States (odds ratio, 3.88 [CI, 1.64 to 9.18]; *P* = 0.002).

Figure 2. **Completion of therapy for latent tuberculosis infection in patients assigned to receive rifampin and pyrazinamide or isoniazid.**



Patients lost to follow-up were those in whom no follow-up data on adherence were available. Treatment was prescribed for 2 months for patients assigned to rifampin and pyrazinamide and 6 months for those assigned to isoniazid. The proportion of patients who completed treatment did not significantly differ between the two groups, even after adjustment for site, age older than 35 years, sex, place of birth, medical conditions, hepatotoxicity, and other adverse events (odds ratio, 1.32 [95% CI, 0.92 to 1.90]; *P* = 0.13).

Percentage of Patients Who Completed Treatment

Although the duration of treatment differed in the isoniazid group and the rifampin plus pyrazinamide group, the proportion of patients who completed treatment was similar (160 of 282 [56.7%] patients vs. 187 of 307 [60.9%] patients, respectively; odds ratio, 1.19 [CI, 0.84 to 1.64]; *P* > 0.2) (**Figure 2**). After adjustment for site, age older than 35 years, sex, place of birth, medical conditions, hepatotoxicity, and other adverse events, the odds ratio for completion of treatment in recipients of rifampin plus pyrazinamide compared with isoniazid recipients was 1.32 (CI, 0.92 to 1.90; *P* = 0.13). Independent risk factors for noncompletion of treatment in the multivariable logistic model were study site 2 (odds ratio, 2.06 [CI, 1.32 to 3.23]; *P* = 0.002) or 3 (odds ratio, 3.48 [CI, 2.19 to 5.53]; *P* < 0.001), grade 3 or 4 hepatotoxicity (odds ratio, 4.85 [CI, 1.61 to 14.7]; *P* = 0.005), and adverse events other than hepatotoxicity (odds ratio, 2.90 [CI, 1.83 to 4.58]; *P* = 0.005). In multivariable analysis, patients who had grade 1 or 2 hepatotoxicity were more likely to complete treatment (odds ratio, 2.81 [CI, 1.45 to 5.45]; *P* = 0.002).

Patients Older Than 35 Years of Age

Among the 213 patients older than 35 years of age at study entry, those who received rifampin and pyrazinamide had a higher risk for grade 3 or 4 hepatotoxicity than did those who received isoniazid (multiple imputation odds ratio, 12.2 [CI, 1.49 to 100.3]; *P* = 0.02). In this subgroup, no statistical difference in the occurrence of nonhepatotoxic adverse events was observed between those who received rifampin and pyrazinamide and those who received isoniazid (odds ratio, 1.09 [CI, 0.59 to 2.03]; *P* >

0.2). The percentage of patients in this subgroup who completed treatment was identical (56%) in both treatment groups but slightly lower than that in younger participants (60%). In multivariable analysis, age older than 35 years may predict noncompletion of treatment (odds ratio, 1.38 [CI, 0.95 to 2.02]; $P = 0.09$).

DISCUSSION

In a group comprising mostly foreign-born adults without HIV infection, 2 months of therapy with rifampin and pyrazinamide for treatment of latent tuberculosis infection was associated with a statistically significantly higher risk for hepatotoxicity than was 6 months of isoniazid therapy. Because of its association with grades 3 and 4 hepatotoxicity, treatment with rifampin and pyrazinamide was also more likely than isoniazid treatment to be discontinued as a result of hepatotoxicity. Although the proportion of nonhepatotoxic adverse events was similar between the two regimens, treatment was discontinued in statistically significantly more recipients of rifampin and pyrazinamide than isoniazid recipients. In addition, although the duration of treatment with rifampin and pyrazinamide was 4 months shorter than that of isoniazid treatment, the percentage of patients who completed treatment was similar in both groups.

Our results suggest that a 2-month regimen of rifampin and pyrazinamide has similar tolerability and acceptability compared with a 6-month regimen of isoniazid. Whether the rifampin and pyrazinamide regimen would be better tolerated and accepted than the currently recommended 9-month regimen cannot be determined from this study. However, because most of the adverse events in the isoniazid regimen, especially hepatotoxicity, occurred relatively early in the course of treatment, it is unlikely that many more adverse events would occur with an additional 3 months of treatment. The percentage of patients who developed grade 4 hepatotoxicity with isoniazid treatment (2 of 282 [0.7%]) is similar to that observed by Nolan and colleagues (20), who reviewed all cases of isoniazid-related hepatotoxicity over 7 years.

Because we studied adverse events and completion of treatment with rifampin plus pyrazinamide or with isoniazid for latent tuberculosis infection, patients underwent regular testing of liver enzymes, which is not usually recommended as part of routine care (11). As a result, we detected most cases of hepatotoxicity on the basis of liver enzyme measurement, and hepatotoxicity was only rarely accompanied by symptoms (4 of 589 patients).

Of note, mild elevation of liver enzyme levels (up to five times the normal value [grade 1 or 2 hepatotoxicity]) does not necessarily indicate that treatment must be stopped. In our study, 35 of 38 (92%) patients who had mildly elevated liver enzyme levels (that is, grade 1 or 2 hepatotoxicity) completed treatment with rifampin and pyrazinamide. Of greater concern are patients who had elevation of serum aminotransferase levels to more than five times normal (grade 3 or 4 hepatotoxicity), in whom treatment was usually discontinued. Although the frequency with which these patients developed symptomatic hepatotoxicity cannot be predicted, hepatotoxicity would have probably progressed if therapy had been continued. In the few published case reports on hepatotoxicity due to regimens containing rifampin and pyrazinamide (12, 13), a common history has been that therapy was continued despite symptoms of hepatitis. Furthermore, because liver enzymes were not routinely measured after 2 months of treatment with rifampin and pyrazinamide, our study may underestimate the incidence of hepatotoxicity with this treatment. Three recipients of rifampin and pyrazinamide developed elevated levels of aminotransferases to greater than five times the normal value (grade 3 hepatotoxicity) at the completion of the second month of treatment, outside the study protocol.

We also found that among persons older than 35 years of age, a group that is at increased risk for hepatotoxicity due to isoniazid therapy, treatment with rifampin and pyrazinamide was associated with increased risk for grades 3 and 4 hepatotoxicity compared with isoniazid. Thus, therapy with rifampin and pyrazinamide may have no particular advantage over isoniazid therapy in persons older than 35 years of age, and persons of this age may be at increased risk for grade 3 or 4 hepatotoxicity. We conclude that patients receiving rifampin and pyrazinamide therapy for latent tuberculosis infection should be monitored closely for any symptoms suggestive of hepatitis. Our results support revised recommendations (13) to include routine follow-up testing of liver enzymes after treatment has begun to screen for hepatotoxicity and thus prevent progression to severe toxicity.

Although experience with rifampin and pyrazinamide for treatment of latent tuberculosis infection in adults without HIV infection is limited, the percentage of patients in our study with hepatotoxicity markedly exceeded that found by Bock and associates (21), who administered these medications to inmates of an urban jail. However, those investigators administered pyrazinamide at a daily dosage of 15 to 20 mg/kg of body weight. In that study, aminotransferase levels were elevated up to 5 times the normal value in 8 of 168 patients, from 5 to 10 times normal in 1 patient, and more than 10 times normal in 1 patient. In three studies of rifampin plus pyrazinamide to treat latent tuberculosis infection in HIV-infected persons (8–10), abnormal liver enzyme levels were seen collectively in only 1% to 3% of patients, a proportion much smaller than in our study. The reasons for these differences are not clear. Possible explanations may include a higher rate of alcohol consumption, higher dosage of pyrazinamide, and older age among our patients, all of which may have predisposed them to drug-induced hepatotoxicity.

Results of previous studies provide some insight into whether rifampin or pyrazinamide might be more likely to be the cause of drug-induced hepatotoxicity. None of 165 patients with silicosis and latent tuberculosis infection in Hong Kong (22) who received rifampin alone for 12 weeks developed hepatitis, and the proportion of patients with an elevated serum ALT level was similar among rifampin recipients and placebo recipients. In contrast, among 22 persons who had contact with a person with multidrug-resistant tuberculosis and were treated with ofloxacin and pyrazinamide (25 mg/kg daily), 5 had a peak serum ALT level of 1 to 5 times normal and 4 had levels of 5 to 10 times normal (23). The potential for higher doses of pyrazinamide to cause hepatotoxicity was clearly demonstrated in early clinical trials (24). Among patients given isoniazid, pyrazinamide (40 mg/kg of body weight), and para-amino salicylic acid to treat tuberculosis, 6.6% developed severe hepatotoxicity. Although we used a lower dosage of pyrazinamide (20 mg/kg daily), these findings taken together suggest that pyrazinamide may be the primary cause of the increased risk for hepatotoxicity that we observed.

Although other nonhepatotoxic adverse events occurred with similar frequency among patients who received rifampin plus pyrazinamide and those who received isoniazid, the percentage of patients in whom therapy was discontinued was significantly greater among those taking rifampin plus pyrazinamide. This is perhaps because clinicians were less comfortable prescribing and managing adverse events associated with this new treatment for latent tuberculosis infection.

In contrast to studies demonstrating a higher rate of completion of therapy among HIV-infected patients taking rifampin and pyrazinamide to treat latent tuberculosis infection (8–10), we found that the percentage of patients who completed this therapy was similar to that of patients who received isoniazid, even though isoniazid therapy required an additional 4 months of administration. A substantial number of patients in both groups did not complete treatment, but the percentage who completed treatment in our study was still higher than that reported by other public health tuberculosis clinics (25). The reasons for the high number of dropouts are not entirely clear, but this finding emphasizes the need for adherence-promoting measures to improve completion of therapy (26). We intentionally did not use any of these adherence-promoting measures so that we could assess the rate of completion among patients who were typical of those seen in urban tuberculosis clinics in the United States and managed in the standard manner.

Our study has limitations. Liver enzymes were not measured in all patients because of loss to follow-up; thus, potential adverse events and hepatotoxicity were not identified in these patients. However, the rate of loss to follow-up was similar in both groups, and the multiple imputation results in which these missing outcomes were estimated from baseline data and treatment assignment were consistent with results in the 411 participants for whom follow-up liver enzyme values were available. Imbalances between groups at baseline included a greater number of patients older than 35 years of age in the isoniazid group, which may have led to an increased risk for hepatotoxicity among isoniazid recipients. However, the risk for hepatotoxicity was higher in patients taking rifampin plus pyrazinamide, and adjustment for this imbalance by using propensity scores did not change the results. Because our study was not blinded, ascertainment bias may have influenced reporting of adherence and adverse events. Finally, we had limited power to examine heterogeneity of treatment effects and clustering by site. However, results for the 411 participants with complete data do not strongly suggest either difficulty.

In summary, administration of rifampin and pyrazinamide for 2 months to treat latent tuberculosis infection was associated with a significantly higher risk for hepatotoxicity, especially grades 3 and 4 hepatotoxicity, than was 6 months of isoniazid therapy in adults without HIV infection. The occurrence of nonhepatotoxic adverse events was similar between the two groups. Although the duration of treatment with rifampin plus pyrazinamide was shorter than the duration of isoniazid treatment, the proportion of patients who completed therapy was similar between groups. Our findings suggest that rifampin and pyrazinamide should be used with caution and support recommendations for frequent laboratory assessment for liver injury after treatment to document early liver injury and prevent progression to severe toxicity.

APPENDIX: THE SHORT-COURSE RIFAMPIN AND PYRAZINAMIDE FOR TUBERCULOSIS INFECTION (SCRIPT) STUDY INVESTIGATORS

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Ximelagatran versus Warfarin for the Prevention of Venous Thromboembolism after Total Knee Arthroplasty

A Randomized, Double-Blind Trial

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Background: **Warfarin is used for prophylaxis of venous thromboembolism in patients undergoing total knee arthroplasty. However, it is associated with rates of deep venous thrombosis (DVT) of approximately 38% to 55% and requires routine coagulation monitoring and frequent dose adjustment. Ximelagatran, an oral direct thrombin inhibitor, has shown promising efficacy and tolerability in patients undergoing total hip or knee arthroplasty.**

Objective: **To compare the efficacy and safety of ximelagatran and warfarin for prophylaxis of venous thromboembolism after total knee arthroplasty.**

Design: **Randomized, double-blind, parallel-group trial.**

Setting: **74 North American hospitals.**

Patients: **680 patients who had undergone total knee arthroplasty.**

Intervention: **7 to 12 days of treatment with oral ximelagatran, 24 mg twice daily, starting on the morning after surgery, or warfarin (target international normalized ratio, 2.5 [range, 1.8 to 3.0]), starting on the evening of the day of surgery.**

Measurements: **Principal end points were asymptomatic DVT on mandatory venography; symptomatic DVT confirmed by ultrasonography or venography; symptomatic, objectively proven pulmonary embolism; and bleeding. All were assessed by blinded adjudication locally and at a central study laboratory.**

Results: **On central adjudication, incidence of venous thromboembolism was 19.2% (53 of 276 patients) in the ximelagatran group and 25.7% (67 of 261 patients) in the warfarin group (difference, −6.5 percentage points [95% CI, −13.5 to 0.6 percentage points]; $P = 0.070$). On local assessment, incidence was 25.4% in the ximelagatran group and 33.5% in the warfarin group ($P = 0.043$). In the ximelagatran and warfarin groups, respectively, major bleeding occurred in 1.7% and 0.9% of patients and minor bleeding occurred in 7.8% and 6.4% of patients. No variables related to bleeding differed significantly between the two groups.**

Conclusions: **For prophylaxis of venous thromboembolism, fixed-dose ximelagatran started the morning after total knee arthroplasty is well tolerated and at least as effective as warfarin, but it does not require coagulation monitoring or dose adjustment.**

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Venous thromboembolism is common after major orthopedic surgery. Meta-analysis has indicated that without prophylaxis, the incidence of deep venous thrombosis (DVT) is 50% to 60% (1). Prophylaxis with low-molecular-weight heparin (LMWH) or warfarin is recommended, but the incidence of venographically confirmed DVT at the time of hospital discharge remains approximately 31% with the former and 47% with the latter (1). In addition, proximal DVT is found in 7% to 12% of patients who receive prophylaxis with either regimen (1). Currently, the use of LMWH and warfarin is approximately evenly divided in North America (2, 3). Warfarin has a slow onset of action and is inconvenient because it requires frequent coagulation monitoring and dose adjustment (3, 4). Low-molecular-weight heparin does not require monitoring but must be administered parenterally, which can be difficult after hospital discharge.

Ximelagatran is a novel oral direct thrombin inhibitor. After administration, it is rapidly absorbed and transformed to its active form, melagatran (5), which provides competitive, direct inhibition of both free and clot-bound thrombin. Administration of ximelagatran results in predictable plasma concentrations of melagatran that increase linearly in relation to dose in healthy volunteers (5) and surgical patients (6, 7). Fixed doses of ximelagatran without coagulation monitoring have been studied in phase II trials and have shown promising results in prophylaxis of venous thromboembolism after total hip or knee arthroplasty (8, 9). In this phase III trial, we compared the efficacy and safety of ximelagatran and warfarin for the prevention of venous thromboembolism after total knee arthroplasty.

METHODS

Study Design

We performed a randomized, double-blind study comparing ximelagatran with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. Patients were recruited from 74 hospitals in the United States and Canada. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board at each hospital. Patients were evaluated for eligibility 1 to 30 days before surgery and were randomly assigned to treatment postoperatively on the day of surgery. Those that appeared to meet the inclusion criteria were approached before surgery to discuss the study and to sign consent forms if they were interested. Those who agreed to participate were reevaluated after surgery and before randomization to ensure that they still met

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entry criteria. Randomization was stratified by unilateral or bilateral surgery at each center and was implemented through an interactive voice response system. Treatment was given for 7 to 12 days, and venography was performed within 12 hours of the final dose. Patients were followed clinically for 4 to 8 weeks after surgery.

Patients

Patients were eligible if they were scheduled for elective total knee arthroplasty, were at least 18 years of age, weighed 40 to 125 kg, and provided consent. Women had to be surgically sterile, postmenopausal for at least 2 years, or using reliable contraception. Criteria for exclusion were scheduled hemiarthroplasty, surface repair, or revisionary surgery; planned external pneumatic compression prophylaxis; immobilization for 3 or more days before surgery; major surgery, ischemic stroke, myocardial infarction, or administration of any investigational drug within 30 days before surgery; a history of intracranial, retroperitoneal, or intraocular bleeding or any other disorder associated with increased risk for bleeding; gastrointestinal bleeding within 90 days before surgery or endoscopically verified ulcer disease within 30 days before surgery; uncontrolled hypertension; cytotoxic treatment for active malignancy; clinically significant liver disease; thrombocytopenia; drug or alcohol abuse in the past 6 months; allergy to contrast media or iodine; contraindication to warfarin; severe renal impairment (defined as estimated creatinine clearance < 0.5 mL/s [<30 mL/min]); or traumatic epidural or spinal puncture before surgery. Metformin was stopped before administration of contrast media for venography and was restarted after 48 hours if renal function was normal. If an epidural or spinal catheter was used, it had to be removed within 36 hours after surgery and at expected trough levels of melagatran. Treatment with thrombolytic drugs and the following anticoagulants or antiplatelet agents was not allowed within 7 days before surgery or during administration of the study drug: heparins, warfarin, dipyridamole, sulfinpyrazone, ticlopidine, clopidogrel, nonselective cyclooxygenase anti-inflammatory drugs with half-life exceeding 20 hours, at least 500 mg of aspirin per day, or dextran.

Treatment Regimens

Tablets containing 24 mg of ximelagatran (AstraZeneca, Wilmington, Delaware) or placebo were given in the morning and evening, with the first dose given on the morning after surgery and at least 12 hours after surgery. Capsules containing warfarin (Coumadin, DuPont Pharmaceuticals, Wilmington, Delaware) or placebo were given each evening, starting on the day of surgery after hemostasis was adequate. Warfarin was started at a minimum dose of 5 mg and was then titrated to achieve a target international normalized ratio (INR) of 2.5 (range, 1.8 to 3.0). Patients remained in the hospital according to local practice, usually for 3 to 4 days, after which they self-administered the medication.

Context

Warfarin is associated with rates of deep venous thrombosis of 38% to 55% when prescribed during total knee arthroplasty and requires frequent monitoring and dose adjustment. The oral thrombin inhibitor ximelagatran has shown promise in prophylaxis of venous thromboembolism in patients undergoing hip and knee arthroplasty. Ximelagatran does not require monitoring or dose adjustment.

Contribution

This randomized, controlled trial compared ximelagatran with warfarin in 680 patients undergoing total knee arthroplasty and found that ximelagatran was at least as effective as warfarin.

Implications

Ximelagatran is an option for prophylaxis of venous thromboembolism in patients undergoing total knee arthroplasty, but this study had limited power to compare adverse effects.

–The Editors

To guide dosing, INRs were measured locally by using a point-of-care device or a laboratory on postoperative days 1 to 3 and as needed in the interim and after discharge until the day of venography. The point-of-care devices were preprogrammed to encrypt INR values, which could be decrypted only by the central anticoagulation management center (Omnicare Clinical Research, Lake Bluff, Illinois). International normalized ratios from local laboratories were reported to the Center, which then faxed real or sham INR values to the investigator. The investigator used these values to determine the next dose of warfarin or placebo. Sham INR values were generated to mimic usual values in persons receiving warfarin. Treatment adherence was assessed by counting tablets and capsules used in the hospital, dispensed at discharge, and returned at the end of the study.

Efficacy Assessments

The primary efficacy variable was the incidence of DVT (proximal or distal) or pulmonary embolism. The secondary efficacy variable was the incidence of proximal DVT or pulmonary embolism. Both variables considered events that occurred during treatment. Deep venous thrombosis was evaluated by ascending venography on the leg or legs that had undergone surgery (10, 11). Standardized film documentation contained no more than nine images per leg. The Central Adjudication Committee assessed venograms for the primary efficacy end point. The criterion for DVT was a consistent intraluminal filling defect on at least two images. Evaluable venograms required visualization of all of the deep veins except the muscular veins and the anterior tibial veins, although DVT was counted if these veins were seen and thrombus was detected. Non-

Table 1. **Overview of the Study Sample**

Variable	Ximelagatran Group	Warfarin Group	Total
	n (%)		
Total patients randomly assigned	348 (100.0)	332 (100.0)	680 (100.0)
Patients who did not receive study medication	3 (0.9)	2 (0.6)	5 (0.7)
Safety sample	345 (99.1)	330 (99.4)	675 (99.3)
Nonevaluable venogram and no confirmed symptomatic venous thromboembolism	69 (19.8)	69 (20.8)	138 (20.3)
Venography not done	36 (10.3)	45 (13.6)	81 (11.9)
Indeterminate results on venography	33 (9.5)	24 (7.2)	57 (8.4)
Efficacy sample	276 (79.3)	261 (78.6)	537 (79.0)

evaluable venograms were defined as those that showed a lack of filling in a region of the deep system of the leg without the presence of an intraluminal filling defect elsewhere in the same region. Ultrasound diagnosis was sufficient for symptomatic proximal DVT, but venography was required for diagnosis of symptomatic distal DVT. Analysis of local interpretations of venograms was included in the statistical analysis plan before unblinding.

Pulmonary embolism was diagnosed when a lung scan showed high probability, defined as one or more segmental perfusion defects seen in at least two views with corresponding normal ventilation. Pulmonary embolism was also diagnosed by pulmonary angiography showing a persistent intraluminal defect or abrupt cutoff of a vessel greater than 2.5 mm in diameter. All cases of suspected pulmonary embolism were adjudicated centrally. Patients with thrombosis were treated according to local practice.

Safety Assessments

All bleeding events were recorded, including bleeding at the site of surgery, volumes of blood loss and transfusion, and wound appearance. Independent experts classified bleeding events as major if they were clinically overt and showed one or more of the following: critical site involvement (intracranial, retroperitoneal, intraocular, intraspinal, or pericardial), bleeding index of 2.0 or greater (calculated as the number of units of red blood cells transfused plus the difference between prebleeding hemoglobin level minus postbleeding event hemoglobin level [g/dL]), medical or surgical intervention at the operative site, or fatal bleeding. The bleeding index provides a measure of hemoglobin change as modified by transfusion and has been used in other studies of prophylaxis after orthopedic procedures (12, 13). Clinically overt bleeding with none of the other characteristics was classified as minor. The investigators also classified the overall appearance and characteristics of the surgical wound as being "as expected," "worse than expected," or "better than expected." Clinical chemistry and hematology variables were assessed at screening, on the last day of study drug administration, and at the 6-week follow-up examination.

Statistical Analysis

Previous studies have shown that deep venous thrombosis occurs in approximately 49% of patients receiving warfarin and in 20% of those receiving ximelagatran (1, 9). To be conservative, and because most venography in our study would be unilateral, we anticipated an incidence of 35% for DVT in the warfarin group. On the basis of these estimates, approximately 480 evaluable patients would be needed to provide 95% power at a 5% significance level to demonstrate superiority of ximelagatran. We selected a sample size of 600 patients, anticipating that 20% would have nonevaluable venograms.

The efficacy analyses included all patients with an evaluable venogram or symptomatic, objectively confirmed DVT or pulmonary embolism during the treatment period. The incidences of total venous thromboembolism and of proximal DVT or pulmonary embolism during treatment were calculated by using the observed rates and 95% CIs in each treatment group; the differences in incidence and 95% CIs were calculated. Group comparisons were tested by using the Cochran–Mantel–Haenszel chi-square test stratified by unilateral or bilateral surgery. Incidences of symptomatic venous thromboembolism and deaths during the follow-up period were also tabulated. Clinical events occurring no more than 2 days after the last dose of study drug were considered to have occurred during treatment; after 2 days, they were considered follow-up events.

The safety analysis included all patients who took at least one dose of study medication. The frequencies and 95% CIs of bleeding events and of individual bleeding complications associated with the surgical wound were analyzed by using methods similar to those used in the efficacy analysis. Appearance of the surgical wound was recorded as the worst appearance noted during the study, and differences were tested by using the Cochran–Mantel–Haenszel chi-square test stratified by unilateral or bilateral surgery. The descriptions of wound appearance were summarized by the percentage of patients for whom each characteristic was "worse than expected." Volumes of operative blood loss, postoperative wound drainage and transfusion, and the bleeding index were estimated by using the means for both treatment groups, and between-treatment differences were tested by using an analysis of variance model blocked by unilateral or bilateral surgery.

Role of the Funding Source

AstraZeneca funded the study and performed all statistical analyses with guidance from the Executive Committee. The Executive Committee, which was composed of six physicians, was involved in study design and monitoring, had full access to the data, and made all decisions regarding publication. A list of the members of the Executive Committee, the Data Safety Monitoring Board, the Central Adjudication Committee, and the site investigators and coordinators can be found in the Appendix (available at www.annals.org).

RESULTS

Patients

Between March and September 2000, 758 patients consented to participate in the study and 680 were randomly assigned to treatment (Table 1). Five patients did not receive study medication for the following reasons: death from myocardial infarction (1 patient in the ximelagatran group), withdrawn consent (1 patient in each group), use of prohibited medication (1 patient in the ximelagatran group), and unfulfilled eligibility criteria (1 patient in the warfarin group). Thus, the safety sample consisted of 345 patients in the ximelagatran group and 330 patients in the warfarin group. Within this sample, 21 patients from the ximelagatran group and 30 from the warfarin group discontinued treatment prematurely because of adverse events (14 and 17 patients, respectively), withdrawn consent (2 and 4 patients, respectively), and "other reasons" (5 and 9 patients, respectively). "Other reasons" in the warfarin group included confirmed pulmonary embolism (3 patients) and confirmed DVT (2 patients). The duration of the treatment was 7 to 9 days for most patients; approximately 25% received treatment for 10 to 12 days. Fewer patients in the ximelagatran group (6%) than in the warfarin group (17%) received treatment for fewer than 6 days, mostly because warfarin therapy was sometimes held to keep INRs in the desired range.

The efficacy sample comprised 276 patients in the ximelagatran group and 261 patients in the warfarin group. One hundred thirty-eight patients (69 in each group) were excluded from the efficacy sample because they had nonevaluable venograms and no confirmed symptomatic DVT or pulmonary embolism. Within the efficacy sample, predefined protocol deviations occurred in 25 patients assigned to ximelagatran and 36 patients assigned to warfarin. Each type of protocol deviation occurred in a similar proportion of patients in either group. Patients with predefined protocol deviations were included in the efficacy analyses. Patient characteristics were well matched (Table 2), and adherence to treatment was approximately 90%.

Thromboembolic Events

When venograms were interpreted centrally, patients receiving ximelagatran had a lower incidence of total ve-

Table 2. **Characteristics of the Safety Sample and the Efficacy Sample***

Characteristic	Ximelagatran Group	Warfarin Group
Safety sample		
Patients, *n*	345	330
Age, *y*	67.8 ± 10.1	67.7 ± 10.4
Women, %	63.2	64.2
Weight, *kg*	87.3 ± 17.7	86.8 ± 18.2
Body mass index, *kg/m²*	31.4 ± 5.9	31.0 ± 6.1
Estimated creatinine clearance, *mL/s (mL/min)*	1.64 ± 0.67 (98.4 ± 40.0)	1.66 ± 0.68 (99.2 ± 40.5)
Ethnicity, *n (%)*		
White	319 (92.5)	302 (91.5)
African American	23 (6.7)	27 (8.2)
Asian	2 (0.6)	1 (0.3)
Other	1 (0.3)	0 (0.0)
Treatment duration, *d*	8.1 ± 2.1	7.7 ± 2.3
Efficacy sample		
Patients, *n*	276	261
History of deep venous thrombosis or pulmonary embolism, *n (%)*	8 (3.0)	9 (3.4)
History of varicose veins, *n (%)*	41 (14.9)	31 (11.9)
Anesthesia, *n (%)*		
General	200 (72.5)	170 (65.1)
Regional	64 (23.2)	75 (28.8)
Other	12 (4.3)	16 (6.1)
Type of surgery, *n (%)*		
Unilateral	257 (93.1)	248 (95.0)
Bilateral	19 (6.9)	13 (5.0)
Tourniquet duration, *min*	70.1 ± 23.9	71.2 ± 25.7
Duration of surgery, *min*	92.5 ± 39.8	87.8 ± 29.6
Time from surgery to first dose, *h*	20.9 ± 4.1	20.8 ± 3.0
Time to ambulation, *d*	1.3 ± 0.6	1.2 ± 0.6
Duration of hospital stay, *d*	5.0 ± 2.8	4.9 ± 2.4
Day of venography	8.6 ± 1.7	8.5 ± 1.6

* Values presented with plus/minus signs are means ± SD.

Table 3. **Incidence of Venous Thrombosis during the Treatment Period***

Event†	Ximelagatran Group	Warfarin Group	Mean Risk Reduction for Ximelagatran vs. Warfarin	P Value‡
	% (n/n)		*percentage points*	
Central interpretation				
Total thromboembolism	19.2 [14.7 to 24.4] (53/276)	25.7 [20.5 to 31.4] (67/261)	−6.5 [−13.5 to 0.6]	0.070
Proximal DVT or PE	3.3 [1.5 to 6.1] (9/274)	5.0 [2.7 to 8.5] (13/258)	−1.8 [−5.2 to 1.6]	>0.2
Local interpretation				
Total thromboembolism	25.4 [20.3 to 31.0] (68/268)	33.5 [27.8 to 39.5] (88/263)	−8.1 [−15.8 to −0.4]	0.043
Proximal DVT or PE	5.7 [3.2 to 9.3] (15/262)	9.2 [5.9 to 13.5] (23/249)	−3.5 [−8.1 to 1.1]	0.119

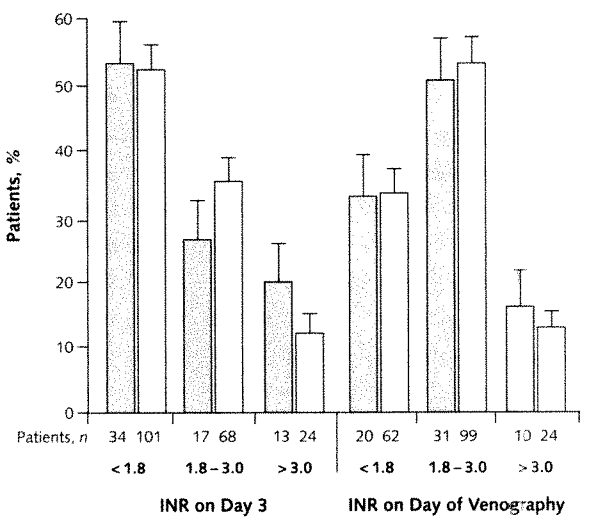
* Numbers in square brackets are 95% CIs. Values in parentheses are numbers of patients/total numbers of evaluable patients. DVT = deep venous thrombosis; PE = pulmonary embolism.

† Total thromboembolism refers to both distal and proximal DVT. Proximal DVT includes only patients with thrombi in the popliteal or more proximal veins.

‡ Treatment differences were tested by using the Cochran–Mantel–Haenszel test, adjusted for type of surgery (unilateral or bilateral).

nous thromboembolism than those treated with warfarin (19.2% vs. 25.7%) (difference, −6.5 percentage points [95% CI, −13.5 to 0.6 percentage points]; $P = 0.070$) (**Table 3**). Both treatments were associated with low incidences of proximal DVT or pulmonary embolism (3.3% in the ximelagatran group vs. 5.0% in the warfarin group; $P > 0.2$). Bilateral surgery was performed in fewer than 10% of patients, and no significant differences were apparent between the overall results for unilateral or bilateral surgery. When venograms were interpreted locally, the incidence of total venous thromboembolism was significantly lower in the ximelagatran group (25.4%) than in the warfarin group (33.5%) ($P = 0.043$). The locally assessed incidences of proximal DVT or pulmonary embolism were 5.7% in the ximelagatran group and 9.2% in the warfarin group ($P = 0.12$). We performed a sensitivity analysis assuming several outcomes in patients without venograms, including 1) that the rate of thrombosis was the overall mean rate or 2) that the rates in ximelagatran- and warfarin-treated patients would be the observed rates in patients who had available venograms. We performed two additional analyses with these same two assumptions but used sex-adjusted rates because of the slightly higher percentage of women without venography in the warfarin group. The analysis was virtually unchanged by these modifications.

Figure. **Presence (*shaded bars*) or absence (*white bars*) of venous thrombosis in patients receiving warfarin, according to international normalized ratio (*INR*) on postoperative day 3 and day of venography.**



Data are means; error bars represent upper bounds of 95% CIs. On day 3, 64 patients had confirmed venous thrombosis and 193 patients did not; on the day of venography, 61 patients had confirmed venous thrombosis and 185 patients did not.

Confirmed symptomatic DVT occurred at similar frequencies in the ximelagatran group (6 of 345 patients [1.7%]) and the warfarin group (6 of 330 patients [1.8%]). During the treatment period, symptomatic pulmonary embolism was confirmed in one patient in the ximelagatran group and four patients in the warfarin group, including one fatal pulmonary embolism on day 3. One additional patient in the ximelagatran group developed symptomatic pulmonary embolism on day 14, 4 days after treatment was stopped. International normalized ratios on day 3 and at venography were not significantly different in patients with or without venous thromboembolism (**Figure**). Approximately one third of patients had INRs in the range of 1.8 to 3.0 at day 3, and one half had INRs in this range at venography. No trend was seen toward a higher rate of venous thromboembolism when INRs were subtherapeutic.

Bleeding

Major bleeding occurred in 6 of 345 patients (1.7%) in the ximelagatran group and 3 of 330 patients (0.9%) in the warfarin group; no statistically significant differences were seen in the rates of bleeding events (**Table 4**). Major bleeding events included gastrointestinal bleeding (3 patients in the ximelagatran group and 1 in the warfarin group) and wound hematomas (3 patients in the ximelagatran group and 2 in the warfarin group). Of the 6 major bleeding events in the ximelagatran group, 5 occurred in the first 3 days, whereas all 3 major bleeding events in the warfarin group occurred more than 7 days after surgery. Transfusion volumes, operative blood loss, postoperative wound drainage, and bleeding indices were similar for both treatment groups. Minor bleeding occurred in 7.8% and 6.4% of patients in the ximelagatran and warfarin groups, respectively.

Wound appearance and bleeding complications were assessed on days 1 to 3, on the day of venography, and at follow-up visits. For all time points combined, overall wound appearance was rated "as expected" in 90% of patients in the ximelagatran group and 92% of patients in the warfarin group and "worse than expected" in 9.9% of patients in the ximelagatran group and 7.9% of patients in the warfarin group. There were no statistically significant differences between treatments at any time. For patients with a "worse than expected" rating at any time, wound appearance was further characterized as due to hematoma, bleeding, unusual bruising, intra-articular bleeding, swelling, drainage, or erythema, and there was no statistically significant difference in any characteristic between the groups. The most common complication was wound bleeding (7.0% of patients in the ximelagatran group and 5.5% of patients in the warfarin group; $P > 0.2$).

Table 4. **Rates of Bleeding Events***

Event	Ximelagatran Group ($n = 345$)	Warfarin Group ($n = 330$)
Major bleeding, %	1.7 (0.6–3.7)	0.9 (0.2–2.6)
Any bleeding, %	9.0 (6.2–12.5)	7.0 (4.5–10.3)
Transfusion, %	38	34
Mean transfusion volume, *U*	0.7 (0.6–0.9)	0.7 (0.6–0.8)
Mean operative blood loss, *mL*†	148 (129–167)	143 (124–163)
Mean postoperative wound drainage, *mL*‡	625 (574–675)	598 (546–651)
Bleeding index§	3.0 (2.9–3.2)	2.9 (2.8–3.1)

* Numbers in parentheses are 95% CIs. $P > 0.2$ for all comparisons. Treatment differences were tested by using the Cochran–Mantel–Haenszel test, adjusted for type of surgery (unilateral or bilateral) and for other variables (analysis of variance blocked by type of surgery).

† Data were available for 323 patients in the ximelagatran group and 311 patients in the warfarin group.

‡ Data were available for 283 patients in the ximelagatran group and 262 patients in the warfarin group.

§ Data were available for 318 patients in the ximelagatran group and 299 patients in the warfarin group. Bleeding index = number of units of blood transfused + (baseline − postvenography hemoglobin value [g/dL]).

DISCUSSION

Our findings indicate that ximelagatran, an oral direct thrombin inhibitor, is at least as effective as adjusted-dose warfarin for prophylaxis of DVT after total knee arthroplasty. Symptomatic DVT was infrequent, and incidences were similar in the ximelagatran and warfarin groups (1.7% and 1.8%, respectively). Symptomatic pulmonary embolism occurred in 0.6% and 1.2%, respectively, of these groups. Efficacy was evaluated by venography between days 7 and 12, when most thrombi are present, and also by clinical evaluation between weeks 4 and 8. Any effect on later events cannot be evaluated. Bleeding complications were infrequent and did not differ significantly in the two groups when assessed by objective or subjective measures.

Venography is the gold standard for diagnosis of venous thromboembolism and was performed only on the operated leg to minimize patient discomfort and risk. In two recent trials, the rates of DVT occurring only in the contralateral leg after total knee arthroplasty were 5.2% (14) and 6.2% (15), indicating that unilateral venography would identify the vast majority of thrombi. Our study prospectively included two blinded interpretations of venography. The central reading was the primary end point and ensured uniformity of interpretation across centers while using strict criteria for interpretation. The local interpretation represented usual clinical practice, had the benefit of fluoroscopy, and may have yielded more readily generalizable results. The results of the two interpretations were generally consistent with each other, but the local interpretation indicated that ximelagatran was statistically significantly more effective than warfarin whereas the central reading showed a trend.

Current guidelines recommend prophylaxis with LMWH or warfarin for patients undergoing total knee arthroplasty, and both treatments are widely used. In six studies directly comparing LMWH with warfarin, the rates of venographically confirmed DVT in patients receiving LMWH ranged from 25% to 45%, with a pooled mean of 31% (1, 14, 16–20). In the corresponding warfarin groups, the rates were 38% to 55%, with a pooled mean of 47% (14, 16–21). Proximal DVT, which is more likely to be symptomatic and associated with pulmonary embolism (22–26), was found in approximately 8% to 12% of patients (21). In our ximelagatran group, the rates of 19.2% and 25.4% for venous thromboembolism on central and local interpretation, respectively, compare favorably with previous results. In a dose-finding study, venous thromboembolism was detected in 16% of patients undergoing total knee arthroplasty in whom ximelagatran, 24 mg twice daily, was started 12 to 24 hours after surgery (9). In a European study, venous thromboembolism was seen in 22% of patients undergoing total knee arthroplasty who received melagatran, 3 mg subcutaneously, before surgery and for 1 to 3 days after surgery, followed by oral ximelagatran, 24 mg twice daily (8). The rates of proximal DVT or pulmonary embolism in the ximelagatran groups of these studies were 3.2% (8) and 2.0% (9), similar to our results.

In our study, the rate of DVT in patients receiving warfarin was lower than that in any other multicenter study and was also lower than the rate of 35% projected in the calculations of sample size. The reason for this is unclear but may be partly related to the use of unilateral rather than bilateral venography. Control of INRs was good, but no clear relation was seen between INR and the occurrence of thrombosis, a finding similar to previous reports (27). Results in our patients receiving ximelagatran were similar to those seen with parenterally administered direct thrombin inhibitors. Rates of DVT of 7% to 18%

have been reported after total hip arthroplasty in patients receiving the recombinant hirudin desirudin (28–30), and venous thromboembolism has been reported to occur in 17% of patients who received bivalirudin after orthopedic procedures (31).

The use of warfarin requires routine coagulation monitoring and dose adjustment because of issues such as drug interactions, diet, concomitant diseases, and varying metabolisms. Furthermore, warfarin has a delayed onset and does not achieve the target anticoagulant level until at least the third postoperative day; this is problematic after orthopedic surgery, when thrombosis may start during the first postoperative day (32). In contrast, ximelagatran is rapidly absorbed and converted to its active form, melagatran (5), which acts directly on thrombin and is eliminated unmetabolized through the kidneys (33). Given in fixed doses, ximelagatran produces predictable plasma melagatran concentrations (5, 7) and has no known food (34, 35) or drug (36–39) interactions. Animal studies indicate that ximelagatran has a wide therapeutic window and increases bleeding only slightly at therapeutic doses (40–42). Melagatran is excreted through the kidney, and plasma concentrations are influenced by renal function and weight in orthopedic patients (43, 44).

Bleeding is a major concern with postoperative anticoagulation, but no statistically significant differences were seen between groups in any measure of bleeding. Other published studies using warfarin in total knee arthroplasty have shown major bleeding in 0.9% (14) and 1.8% (17) of patients, similar to the rates observed in our study; slightly higher rates of 2.8% (14) and 2.1% (17) were seen in the comparator groups receiving LMWH. We performed a detailed analysis of complications at the surgical site, taking particular care to assess wound bleeding and appearance because surgeons are often concerned about wound healing in the presence of antithrombotic therapy. No differences in wound complications were observed.

In summary, in this randomized trial, postoperative ximelagatran was effective and well tolerated for prevention of venous thromboembolism. It was at least as effective as adjusted-dose warfarin, and no differences were seen in bleeding or wound complications between groups. Fixed oral doses of ximelagatran without routine coagulation monitoring or dose adjustment seem to be suitable for thromboprophylaxis after total knee arthroplasty.

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Relationship between Levels of Indinavir in Hair and Virologic Response to Highly Active Antiretroviral Therapy

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Background: **Suboptimal levels of antiretroviral drugs result in virologic failure in HIV-infected patients treated with highly active antiretroviral therapy (HAART).**

Objective: **To assess the relationship between levels of indinavir in hair and virologic outcome.**

Design: **Cross-sectional study.**

Setting: **7 AIDS clinics in France.**

Patients: **89 HIV-infected patients who received HAART that included indinavir.**

Measurements: **Patients were classified as responders or nonresponders on the basis of viremia at the time of hair collection. In nonresponders, levels of indinavir in hair and resistance mutations in the protease gene were assessed at baseline and at the time of indinavir measurement.**

Results: **Mean indinavir levels (±SD) were significantly higher in the 65 responders than in the 24 nonresponders (24.4 ± 16 μg/g vs. 12.9 ± 8.6 μg/g) ($P < 0.001$). Nonresponders with intermediate levels of indinavir in hair had more mutations in the protease gene than did nonresponders with low levels of indinavir in hair.**

Conclusion: **Indinavir levels in hair are associated with virologic outcome in patients receiving HAART.**

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See editorial comment on pp 696-697.

Highly active antiretroviral therapy (HAART) reduces morbidity and mortality from HIV-1 infection (1, 2). Long-term efficacy of HAART depends on strict adherence to prescribed regimens. Suboptimal drug levels are associated with emergence of drug-resistant HIV-1 variants and therapeutic failure (3–6). Because most antiretroviral drugs have a short half-life, monitoring serum and urine levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors reflects only the last doses ingested (7, 8). The pharmacokinetics of long-term HAART remain unclear because of the failure to adequately monitor antiretroviral treatment. In a small study, we previously showed that indinavir concentrations in hair samples are significantly higher in responders to HAART than in nonresponders (9). Hair growth varies from 0.5 to 1.5 cm each month in individual patients, and a monthly history of circulating drugs can be ascertained from the distribution of drug concentration in hair, which is done with a test called a *capillogram* (10–13). In the current study, we assessed the association among levels of indinavir in hair, virologic response, and the emergence of drug-resistant variants.

METHODS

Patient Sample

One hundred four consecutive drug-naive outpatients gave informed consent and were enrolled in seven clinics that treated AIDS. Before patients began receiving HAART, baseline plasma HIV RNA levels and CD4 cell counts were determined, and plasma samples were separated into aliquots and stored at −80 °C. The HAART regimen was indinavir, 800 mg three times daily, and two non-nucleoside reverse transcriptase inhibitors. Indinavir levels were tested only after a patient had received HAART for a minimum of 3 months.

Testing Indinavir Concentrations in Hair

A small piece of hair (approximately 4 mm in diameter) was cut near the scalp on the neck, leaving an almost undetectable line. If sufficiently long, hair samples were cut into 2-cm segments, frozen at −20 °C, and crushed into a powder by an electromagnetic bar (Spex, BioBlock, Paris, France). Indinavir concentrations were determined by using modified high-performance liquid chromatography with a column-switching procedure (8). Eight hair segments from healthy volunteers who were not taking any medications served as controls. The indinavir calibration curves were linear in the range of 2.5 to 100 μg/g ($R^2 >$ 0.99). Limit of quantification was 0.5 μg/g.

Virologic Response and Indinavir Drug Resistance Analysis

On the day of hair sampling, patients with a plasma HIV RNA level below the threshold of the assay (500 copies/mL) (Quantiplex HIV-1 RNA 3.0 assay, Chiron Diagnostics Corp., Emeryville, California) were classified as responders. The protease gene was sequenced in paired plasma samples from nonresponders at baseline and on the day of hair sampling. Plasma viral RNA was extracted, and relevant mutations were determined by direct sequencing on reverse transcriptase polymerase chain reaction products (ABI310, Applied Biosystems, Foster City, California). The mutations involved alteration of protease amino acid residues M-46 (to I or L), V-82 (to A, F, S, or T), L-90 (to M), or I-84 (to V), alone or in combination with two minor mutations at residues L-10 (to I), K-20 (to R),

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M-36 (to I), I-54 (to V or L), A-71 (to V or T), or G-73 (to s) (14–16). Three groups of patients were identified: responders, nonresponders with drug-resistant variants, and nonresponders with indinavir wild-type virus.

Statistical Analysis

Basic descriptions of the clinical and biological variables are expressed as the mean (±SD). These variables were compared by using the Student t-test and, when the sample size was small, by using the Mann–Whitney U test. The main analysis compared indinavir concentrations in responders and nonresponders by using the Student t-test. In the secondary analyses, we compared indinavir concentrations in nonresponders with mutations and nonresponders without mutations by using the Student t-test. Then, we determined the indinavir concentration that best distinguished these groups of nonresponders from one another by using empirical receiver-operating characteristic curves. The threshold was defined graphically as the best combination of sensitivity and specificity. Finally, indinavir concentration along hair was modeled by using a multivariate regression model that accounted for all available indinavir concentrations. This model included the following fixed effects: Patient group, hair segment number, indinavir treatment duration, and first-order interaction terms. Model and interaction terms were created by assuming a linear relationship, except for patient group. The model took into account clustering by patient. P values of the fixed effects were computed by using the asymptotically consistent estimator method (17). Calculations were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

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RESULTS

Baseline Characteristics

Of the 104 patients enrolled in the study, 13 were excluded because their hair samples were less than 2 cm in length, and 2 were lost to follow-up. Of the remaining 89 patients (65 men and 24 women) included in the analysis, 65 were classified as responders (73%) and 24 were classified as nonresponders (27%). At baseline, responders and nonresponders were similar in age, ethnicity (all patients were white), CD4 cell counts, HIV RNA copies, months of indinavir therapy at the time of hair analysis, and reverse transcriptase inhibitors used in their HAART regimens. The mean duration of indinavir treatment (±SD) was 14.1 ± 7.0 months.

Testing Indinavir Levels in Hair

The mean length of hair samples was 3.8 cm (range, 0 to 10 cm). After hair segments were cut, 170 2-cm segments were recovered: 89 scalp-proximal segments (range, 0 to 2 cm), 35 second segments (range, 2 to 4 cm), 20 third segments (range, 4 to 6 cm), 16 fourth segments (range, 6 to 8 cm), and 10 fifth segments (range, 8 to 10 cm. As shown in **Figure 1**, mean indinavir concentrations (±SD) in the proximal segments were significantly higher in responders than in nonresponders (24.4 ± 16.0 μg/g vs. 12.9 ± 8.6 μg/g) ($P < 0.001$) (**Figure 1**) and in the second 2-cm segments (24.4 ± 17.1 μg/g vs. 10.6 ± 7.2 μg/g) ($P = 0.016$). Mean indinavir concentrations were also higher in responders than in nonresponders in the third 2-cm segments (13.7 ± 8.7 μg/g vs. 9 ± 6.2 μg/g) and the fourth 2-cm segments (9.7 ± 7.9 μg/g vs. 9.0 ± 4.7 μg/g). The difference was not significant, however, probably because of the small sample size.

Context

Current methods for monitoring adherence to and the pharmacokinetics of highly active antiretroviral therapy (HAART) are inefficient and inaccurate. Patient reports tend to overestimate adherence, and blood levels reflect only the medication doses given most recently. A preliminary study suggested that indinavir levels in hair samples were higher in HIV-infected patients who responded to HAART than they were in nonresponders.

Contribution

This study confirms that indinavir levels in hair are higher in responders to HAART than in nonresponders. Intermediate levels of indinavir in hair were associated with drug-resistant variants of the virus.

Implications

Measurement of hair levels of antiretroviral drugs deserves further evaluation to establish its role in monitoring HIV-infected patients receiving HAART.

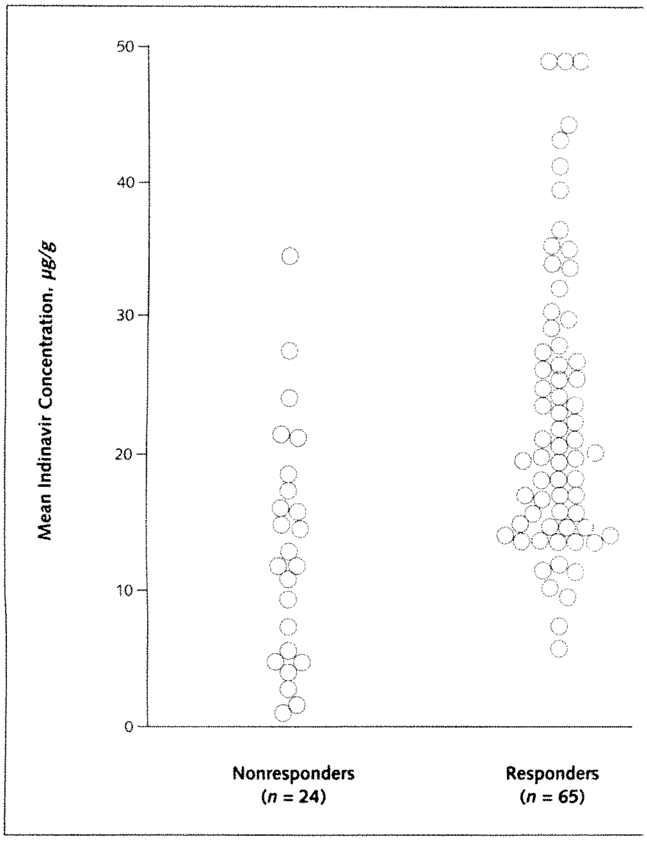
–The Editors

Resistance Analysis

We evaluated genotype resistance to indinavir in 21 of the 24 nonresponders (87%); 2 samples were inadequate, and 1 sample could not be amplified. At baseline, before HAART was initiated, only 1 nonresponder had a drug-resistant HIV-1 variant (mutations M-46 [I to L] and L-90 [to M]). This patient had the highest indinavir concentration among all nonresponders. Twelve nonresponders harbored indinavir-resistant HIV-1 variants, and nine nonresponders harbored indinavir-susceptible HIV-1 variants. The nonresponders with indinavir-resistant HIV-1 variants had higher mean indinavir levels than did the nonresponders with no mutations (14.5 ± 8.4 μg/g vs. 8.5 ± 7.9 μg/g [$P = 0.075$] in the first 2-cm segments, 17.9 ± 4.8 μg/g vs. 7.0 ± 4.1 μg/g [$P = 0.03$] in the second 2-cm segments, and 14.4 ± 0.1 μg/g vs. 6.3 ± 5.9 μg/g [$P = 0.15$] in the third 2-cm segments).

Figure 2 shows an empirical receiver-operating charac-

Figure 1. **Mean indinavir concentration in the first 2-cm segment of hair in patients who responded or did not respond to highly active antiretroviral therapy that included indinavir.**



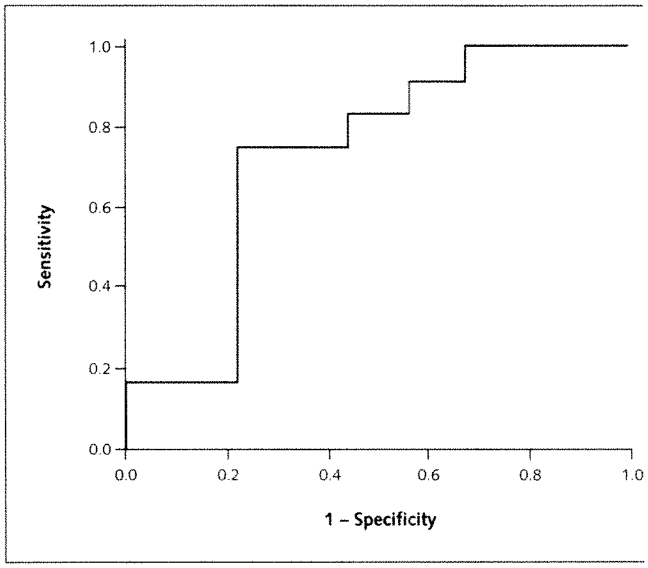
teristic curve, using indinavir concentration in the first hair segment. A threshold of 11.4 μg/g distinguished patients with resistant HIV-1 variants from those who did not have resistant HIV variants; the threshold corresponds to a sensitivity of 0.75, a specificity of 0.78, a positive predictive value of 0.82, and a negative predictive value of 0.70. Multivariate regression analysis, which included all available hair segment concentrations in a single model, revealed that the overall mean concentrations of indinavir in hair (±SD) differed significantly among responders (22.1 ± 2.6 μg/g), nonresponders with mutations (14.0 ± 3.7 μg/g), and nonresponders without mutations (8.5 ± 3.9 μg/g) ($P < 0.001$). In addition, the overall mean concentration of indinavir was significantly lower in samples that were farther from the scalp (decrease, 5.0 ± 0.9 μg/g from one hair segment to the next) ($P < 0.001$). The magnitude of this decrease along the length of the hair was significantly reduced by 0.2 ± 0.1 μg/g for every month that indinavir treatment continued ($P = 0.01$). In nonresponders with mutations, the magnitude of this decrease along the length of the hair was further reduced by 2.7 ± 1.0 μg/g compared with patients in the other groups ($P < 0.001$). No other statistically significant effect or interaction was found to be associated with indinavir concentrations in hair.

DISCUSSION

During long-term therapy with HAART, the main factors that influence drug effectiveness are adherence, drug absorption, and clearance (3, 4, 7, 18). Our study demonstrates that indinavir concentrations in hair samples are significantly higher in HIV-infected patients who respond to HAART than in those who do not respond. Intermediate indinavir concentrations in nonresponders were associated with the emergence of indinavir-resistant variants, possibly because of irregular or decreased absorption or nonadherence. Our results agree with those from a report that demonstrated a relationship between resistance and drug levels (18). In contrast, low concentrations of indinavir in hair of nonresponders were not associated with the emergence of indinavir-resistant HIV-1 variants. Possible reasons for the low drug concentrations included decreased absorption or patient nonadherence. Regardless, low concentrations were an insufficient stimulus for the development of drug-resistant strains. Before a second-line rescue treatment is initiated for nonresponders with low concentrations of indinavir, an in-depth clinical evaluation of adherence and a search for potential reasons for decreased absorption should be done (9). Responders exhibited progressive clearance of indinavir from proximal to distal hair segments. In nonresponders with wild-type virus, levels of indinavir in hair were lowest in hair samples farthest from the scalp, suggesting continued nonadherence. The smaller magnitude of indinavir clearance in nonresponders with mutated HIV strains could indicate erratic adherence.

Testing indinavir levels in hair seems to be a simple, safe, and inexpensive (approximately $25) method for eval-

Figure 2. **Receiver-operating characteristic curve of indinavir concentrations in the first 2-cm segment of hair in nonresponders with HIV mutations and nonresponders without HIV mutations (area under the curve, 0).**



uating indinavir intake and absorption over a period of months. This technique deserves evaluation in larger clinical trials to establish its role in the care of HIV-infected patients receiving HAART.

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Ethical Considerations of Complementary and Alternative Medical Therapies in Conventional Medical Settings

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Increasing use of complementary and alternative medical (CAM) therapies by patients, health care providers, and institutions has made it imperative that physicians consider their ethical obligations when recommending, tolerating, or proscribing these therapies. The authors present a risk–benefit framework that can be applied to determine the appropriateness of using CAM therapies in various clinical scenarios. The major relevant issues are the severity and acuteness of illness; the curability of the illness by conventional forms of treatment; the degree of invasiveness, associated toxicities, and side effects of the conventional treatment; the availability and quality of evidence of utility and safety of the desired CAM treatment; the level of understanding of risks and benefits of the CAM treatment combined with the patient's knowing and voluntary acceptance of those risks; and the patient's persistence of intention to use CAM therapies. Even in the absence of scientific evidence for CAM therapies, by considering these relevant issues, providers can formulate a plan that is clinically sound, ethically appropriate, and targeted to the unique circumstances of individual patients. Physicians are encouraged to remain engaged in problem-solving with their patients and to attempt to elucidate and clarify the patient's core values and beliefs when counseling about CAM therapies.

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Because the use of complementary and alternative medical (CAM) therapies is becoming increasingly widespread in the United States (1, 2), physicians with traditional training now confront a complex array of ethical dilemmas. The conventional physician in the United States is relatively unfamiliar with CAM therapies, a lack of consensus exists among orthodox health care providers about CAM use within conventional medicine, and scientific evidence for CAM therapies is rapidly shifting. Such an environment creates a potential for serious physician–patient conflict, as well as patient harm, when CAM and conventional medical therapies intersect (3–5). Some CAM therapies in and of themselves can be hazardous, but harm can also occur indirectly when patients choose less effective CAM treatments instead of conventional methods that have demonstrated efficacy. In individual situations in which evidence supporting CAM therapies is good, more subtle forms of harm can manifest when a provider, either through bias against such therapies or lack of knowledge, presents conventional treatment as the only available option. In such situations, a patient could be deprived of potentially useful CAM treatments, may be unable to actively participate in decision making, and may be left without medical supervision and monitoring while using CAM therapies.

Physician–patient conflict may also occur when the patient considers the use of CAM treatments that are not supported by evidence-based medicine. Although some CAM therapies have been subjected to randomized, controlled trials, evidence for many types of CAM therapies is quite thin or simply does not exist. Some of these therapies also have a strong spiritual component that relates directly to a person's belief system, and some patients choose such treatments despite a lack of evidence of benefit—or worse, despite clear evidence that such treatments are ineffective. The challenge for physicians in such situations is to provide ethical, medically responsible counseling that respects and acknowledges the patient's values. Physicians should not violate their own values in the process of responding to a patient's needs or abandon the practice of evidence-based medicine in order to provide support for their patients' beliefs. A long-standing, carefully nurtured partnership between physician and patient that has grown over time may be strained or completely destroyed if common ground in such situations cannot be found. Choosing to withdraw from care of a patient because of a fundamental conflict is a decision that requires intense self-examination by the physician and consultation with trusted colleagues; it is a decision that is never made lightly (6). Physician–patient conflict arising from issues related to use of CAM therapies is common, but the need to withdraw from care should be rare if physicians are willing to engage creatively with patients when problems seem unsolvable (7, 8). However, even physicians who are willing to consider CAM treatments in some circumstances find it difficult to know how to responsibly and ethically advise patients in this unfamiliar realm of medicine. They feel uninformed about CAM therapies and ill-equipped to judge the quality of CAM providers.

We present two prototypical cases that illustrate the challenges already discussed as well as other ethical challenges that will arise as use of CAM therapies in the United States becomes even more common. The use of case-based reasoning, or casuistry, in questions of CAM therapy use allows a fuller appreciation of the way in which circumstances play an intrinsic role in moral judgments (9, 10). Specific details of each case are particularly relevant in guiding ethical decision making (**Table**). This information forms a risk–benefit framework in which varying degrees of illness, efficacy, safety, and patient choice help guide a conventional physician to recommend, tolerate, or proscribe the use of CAM therapies. Application of this familiar type of risk–benefit analysis to questions of CAM use can help providers develop a treatment plan that responsi-

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bly fulfills their ethical obligations while recognizing and allowing consideration of the unique circumstances of each case.

CASE 1

Ms. P., a 52-year-old woman, sees a naturopath for her primary care. The naturopath refers Ms. P. to a gynecologist for evaluation of an abnormal Papanicolaou smear performed at an annual examination in the naturopath's office. Cervical biopsies reveal adenocarcinoma in situ, a premalignant condition that, if left untreated, can progress to invasive adenocarcinoma. The gynecologist recommends a cervical conization or hysterectomy to ensure that all abnormal tissue is identified and removed. Ms. P. is a Reiki practitioner, trained to perform a type of energy healing that is said to involve moving energy through the body in order to balance it. She tells the physician that she plans to pursue meditation, colonics, and yoga and to work with her Reiki master rather than have surgery. She further states that she does not want any "surgical invasion of her bodily integrity." The gynecologist feels unable to change Ms. P.'s mind, is concerned about her prognosis, and is unsure about remaining in the physician–patient relationship.

Analysis of this case begins with consideration of the factors presented in the Table. Ms. P. has a precancerous condition that, if left untreated, has a high likelihood of progressing to invasive cancer within several years. The conventional treatment offered is admittedly invasive but at this point should be completely curative. Ms. P. is highly motivated to seek CAM therapies, but although there are some data on the beneficial effect of her chosen treatments for some conditions (11, 12), no data support successful treatment of a precancerous condition. In addition, these treatments are generally used to increase overall well-being rather than to cure a specific physiologic abnormality.

Ms. P. is legally competent; the law presumes persons are competent unless a judge has ruled them incompetent. However, a physician faced with a seeming inexplicable decision by a patient must explore the patient's capacity for decision making. Capacity requires at least an ability to understand relevant information, to appreciate one's medical choices and their possible consequences, to communicate a choice, and to engage in rational deliberation about one's own values in relation to the physician's recommendations about treatment options (13). Review of Ms. P.'s records showed that she had no psychiatric history, but that she had been sexually abused as a child and, as an adult, had received counseling regarding this history. She had been practicing for the previous 4 years as a Reiki therapist, trained to move energy throughout the body in a way that is said to provide balance and healing. Ms. P. exhibited no verbal or behavioral signs of mental illness.

Once the physician was satisfied that the patient's decision-making capacity was adequate, the physician had to ensure that Ms. P. was fully informed by carefully explaining the potential risks involved and attempting to persuade her to change her mind. The physician approached the patient by saying, "As far as I am able to tell, you don't have cancer now, but the condition you have often does progress to cancer, and the more time that passes before you have these cells removed, the more likely it is that they eventually will turn into cancer. I'm concerned that if you delay treatment by trying some of these other methods, none of which have been shown to be effective in treating your condition, you may end up with cancer, which will be much more difficult, if not impossible, to cure." The patient should show understanding of the risks, a willingness and ability to communicate about them, and a capacity to rationally deliberate.

Table. **Factors in Risk–Benefit Analysis of Complementary and Alternative Versus Conventional Medical Treatment***

Severity and acuteness of illness
Curability with conventional treatment
Degree of invasiveness, associated toxicities, and side effects of conventional treatment
Quality of evidence of safety and efficacy of the desired CAM treatment
Degree of understanding of the risks and benefits of CAM treatment
Knowledge and voluntary acceptance of those risks by the patient
Persistence of the patient's intention to use CAM treatment

* CAM = complementary and alternative medical.

Ms. P. listened carefully to everything the physician said, and, as the physician listened equally intently, it became clear to him that Ms. P.'s choice reflected her values of noninvasion of the body; belief in the body's ability to heal itself; and the importance of the relationship between illness and mental, emotional, and spiritual health. Although she had had chaotic and difficult early years, Ms. P. had found solace and peacefulness in her beliefs, which influenced every part of her life. She not only practiced Reiki herself but taught the techniques to others and had even established a newsletter that was circulated among other Reiki practitioners and their clients. At one point, Ms. P. stated firmly and calmly, "Even if you told me I would die next month without surgery, I still wouldn't have it." The physician began to feel that not only would any further attempt to convince Ms. P. to undergo surgery be disrespectful of these deeply held core values, but that her internal sense of integrity could be irretrievably harmed were she to undergo a procedure that was not congruent with her beliefs.

As a general principle, the personal beliefs and choices of other persons should be respected if they pose no threat to other parties (13). The dilemma for the physician in this case became whether to continue providing care for Ms. P. when it was clear that her values were deeply held and durable: There was really no expectation that she would change her mind and agree to the physician's recommendation. The resolution in this case was relatively straightforward. Because Ms. P. had seen the gynecologist only in consultation, she was free to reject the recommendation for surgery and return to her naturopath for continued medical care, with an invitation to return to the physician if she desired further discussion. Informed refusal of care was carefully documented, and the physician contacted the naturopath, who felt able to continue to provide care for Ms. P. despite her refusal of surgery.

The question of withdrawal from care becomes more difficult when the physician in question is the patient's primary care provider; in this situation, the ongoing relationship with the patient must be considered. The ethical obligation of nonabandonment emphasizes the longitudinal nature of a caring commitment between physician and patient. The promise to face the future together is a central obligation of the physician–patient relationship, which carries with it a commitment by the physician to jointly seek solutions with patients throughout their illnesses (6, 14, 15). The limits of this obligation will vary, depending on such things as the length of time of the relationship, the patient's other medical conditions, and the patient's desire for continued care from this physician. Ms. P.'s refusal of surgery may be seen by some physicians as an understandable—albeit incorrect—decision, given the totality of her circumstances. These physicians would feel able to continue as her primary care provider. In the case of Ms. P., the physician should explain his viewpoint—that he considers her decision a serious mistake but is willing to continue providing long-term care for her, even if she develops cancer. Others may find her decision unsupportable, feeling that continuing to provide care would involve giving tacit approval to an irresponsible decision. Such physicians would opt to withdraw from her care and make a referral to a more like-minded physician. But the obligation of nonabandonment challenges us to meet and engage with our patients in conflicts, not shy away from them by recourse to unbending rules or blindly following some imaginary, clearcut boundary about what is acceptable or unacceptable (6). Patients do not always expect medical solutions to their problems, and withdrawal of care should happen only when the physician's own values compel such a decision. Physicians who feel that remaining in the relationship provides false reassurance to the patient should review the patient's decision-making process (and remind themselves that the patient came to this choice with full awareness of the possible consequences) and should avoid overemphasizing their own role as the patient carries out his or her decision.

CASE 2

Ms. L., a 48-year-old woman with recurrent metastatic ovarian adenocarcinoma, seeks an oncologist who will provide her with conventional treatment but is open to the use of CAM treatments as adjunctive therapy. She wants her provider to assist her in evaluating available CAM treatments and give guidance about their appropriateness for her. She raises the issue with her oncologist, who dismisses the subject, explaining that she cannot recommend CAM treatments because they have not been subjected to scientific scrutiny and that the patient is risking her health in seeking these types of care. The physician further comments that if there were any evidence that CAM therapies could help, she would offer them herself. Ms. L. cannot switch providers because her insurance plan requires she be seen by this oncologist, and she feels frustrated in her attempts to engage with her physician in this aspect of her care.

Ms. L. has requested information regarding the effectiveness of CAM treatments as an adjunct to, not as a substitute for, the planned conventional treatment of her metastatic cancer. Her oncologist states that there is no evidence that any CAM therapies are useful in this regard. Actually, however, data support the use of various types of CAM treatments for patients with cancer. For example, the positive effects of relaxation training for improving anxiety and decreasing pain (16); of acupuncture for diminishing nausea associated with chemotherapy (17); and of psychotherapy, group therapy, relaxation, and imagery for improving the quality of life in patients with breast cancer (18) have all been suggested through controlled trials. In contrast, many herbal and metabolic regimens that have been proposed for the primary treatment of cancer are currently not supported by scientific evidence (19). The other relevant factors in this case are that Ms. L.'s condition is chronic and severe, with a low expectation of cure with traditional methods, and that she is highly motivated to use CAM therapies, which may improve her quality of life. In undertaking CAM treatments, she may also regain some sense of control over her physical, psychological, and spiritual health. Also of importance is that she is actively seeking the guidance and advice of her conventional caregiver.

In such a situation, the patient's choice of CAM therapies should be respected. The increasing body of research regarding the effectiveness of some types of CAM therapies (19–21) helps clinicians to judge the advisability of these therapies according to the following criteria. As suggested by other authors, in making such judgments, consideration should be given to whether available evidence 1) supports both safety and efficacy; 2) supports safety but is inconclusive about efficacy; 3) supports efficacy but is inconclusive about safety; or 4) indicates either serious risk or inefficacy (22).

If evidence supports both safety and efficacy, the physician should recommend the therapy but continue to monitor the patient conventionally. If evidence supports safety but is inconclusive about efficacy, the treatment should be cautiously tolerated and monitored for effectiveness. If evidence supports efficacy but is inconclusive about safety, the therapy still could be tolerated and monitored closely for safety. Finally, therapies for which evidence indicates either serious risk or inefficacy obviously should be avoided and patients actively discouraged from pursuing such a course of treatment. This risk framework for CAM therapies allows the physician to make a thoughtful decision that will be evidence based, ethically appropriate, and legally reasonable (22). In the case of Ms. L., the oncologist could therefore reasonably respond to the patient's request for guidance about CAM therapies by considering acupuncture for the patient's chemotherapy-associated nausea and mind–body techniques, such as relaxation and imagery, for anxiety and pain.

It is not difficult for a physician to counsel a patient about CAM therapies for which evidence exists. No one would disagree that physicians should be aware of pertinent evidence and be willing to consider any intervention, CAM or allopathic, that has an acceptable risk–benefit balance; apprise the patient of acceptable options; and make a recommendation. In fact, the obligation of informed consent requires that physicians raise and discuss CAM therapy options that have been shown to be efficacious (23). An example of one such option is lifestyle programs that include yoga, meditation, exercise, and dietary changes for the treatment of heart disease (11). Likewise, a physician should take the initiative to proactively steer patients away from treatments that are known to be dangerous or have been associated with clinically significant adverse interactions with other supplements or medications (24–26). CAM therapies have become so common that inquiries about their use should become a routine part of history taking (27).

There are currently many situations for which no reliable evidence about CAM therapies exists but patients nonetheless request these treatments; in such cases, physicians must counsel and advise in the absence of evidence. When there is no evidence either for or against a particular therapy, physicians can choose to tolerate and monitor or actively discourage use of CAM treatments. The risk–benefit framework presented in the Table is helpful in counseling because the unknown CAM therapy can be compared with what is known about the competing conventional treatment and the relative risk of choosing the CAM therapy can be assessed. If, for example, the conventional treatment is effective and the risk for not treating is great, a patient would be ill-advised to pursue an unproven CAM therapy, and the physician should actively discourage such a decision. If, however, the standard conventional therapy is ineffective, even an unproven CAM therapy could be tolerated, because the patient has few, if any, good alternatives. An unproven therapy may have unknown toxicities, and patients should be clearly informed about the lack of information on the safety of untested CAM therapies, particularly if the condition being treated is minor.

Such discussions between physician and patient are the heart of informed consent, and a physician's recommendations are often the beginning rather than the ending of an exchange that will ultimately determine the course the patient chooses. It can be helpful to begin the discussion by focusing on general goals of treatment (for example, care vs. cure) rather than moving immediately to a consideration of specific interventions, which may lead the patient to prematurely choose therapy that may not serve his or her ultimate goals well (28). The final choice of treatment belongs to the patient and should reflect his or her beliefs and values; physicians should seriously consider and try to respond to the patient's needs to the fullest possible extent without violating their own values. For example, if Ms. L. refused chemotherapy in favor of some unproven herbal preparation, the approach should be similar to that of the physician caring for Ms. P. She and her physician should first attempt to reach a common understanding of the nature of her condition, her prognosis, and the goals of treatment. If she persisted in rejecting chemotherapy, her physician would have an appreciation of the reasons supporting this choice and would hopefully feel able to provide Ms. L. with a continued open-ended commitment to long-term joint problem-solving despite her refusal of conventional care (6).

Physicians routinely refer patients to other practitioners and can be expected to be able to judge the skill of their physician colleagues; however, physicians with no training in a particular complementary therapy, such as acupuncture, will find it difficult to be a reasonable judge of CAM providers. Therefore, it is of paramount importance that physicians have some understanding of currently existing methods of credentialing various types of CAM providers (29) as well as the potential liability associated with these referral relationships (22, 30). The reader is referred to the considerations of credentialing CAM providers and malpractice liability associated with CAM discussed elsewhere in this series (22, 29).

CONCLUSION

Increasing use of CAM therapies in the United States provides an opportunity to reexamine the ethical foundations of western medical practice with renewed attention to the commitment physicians make when entering into a caring relationship with a patient. Physicians routinely balance risks and benefits in decision making, but the advent of CAM therapies challenges physicians to deal responsibly with paradigms of healing that fall outside the boundaries of conventional medical practice and to make decisions in these unfamiliar realms, often in the absence of evidence. Specific details of each case should be factored into a risk–benefit assessment so that a plan of treatment that is clinically reasonable and ethically appropriate can be developed.

The commitment to joint problem solving over time that is a central obligation of the physician–patient relationship becomes even more important when considering the use of CAM therapies. Elucidating patients' experiences of illness, their hopes and values, and what they see as their best interests is vital if physicians and patients are to find common ground when making decisions in areas of uncertainty. As the body of evidence regarding CAM therapies grows, we hope that the model of decision making we have presented will provide an ethical structure for medical practice in which physicians routinely combine the powerful tools of conventional medicine with those CAM therapies shown to be worthy of clinical integration.

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QUALITY GRAND ROUNDS
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Hospital-Onset Infections: A Patient Safety Issue

Julie Louise Gerberding, MD, MPH*

Hospital-onset infections, particularly those involving the urinary tract, lung, and bloodstream, are common and costly and cause substantial morbidity. This article analyzes the case of a 78-year-old man with lung cancer who died after developing hospital-onset pneumonia and urinary catheter-related infection during hospitalization for elective removal of a cerebellar metastasis.

The field of infection control could benefit by adopting several approaches advocated by patient safety adherents, such as root-cause analysis. For example, hospital-onset infections that are implicated as attributable causes of death should perhaps be reviewed by local infection control teams regardless of the institution's overall infection rates. The patient safety movement can also learn from the traditions of infection control and hospital epidemiology. Specifically, applying infection control–based practices to safety problems may enhance safety. Such practices include establishing clear definitions of adverse events, standardizing methods for detecting and reporting events, creating appropriate rate adjustments for case-mix differences, instituting evidence-based intervention programs, and relying on skilled professionals to promote ongoing improvements in care.

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"Quality Grand Rounds" is a series of articles and companion conferences designed to explore a range of quality issues and medical errors. Presenting actual cases drawn from institutions around the United States, the articles integrate traditional medical case histories with results of root-cause analyses and, where appropriate, anonymous interviews with the involved patients, physicians, nurses, and risk managers. Cases do not come from the discussants' home institutions.

CHRONOLOGY OF EVENTS

Tom Reilly (a pseudonym), a 78-year-old man with stage IV non–small-cell lung cancer and chronic obstructive pulmonary disease, developed several infections during hospitalization for elective surgical resection of a single cerebellar metastasis. On the day of his surgery, Mr. Reilly was brought to the operating room, where an arterial line, a standard Foley catheter, and two large-gauge peripheral intravenous lines were placed and a single intravenous dose of vancomycin was administered. An oral endotracheal tube was inserted. A craniotomy was performed, and a cerebellar mass, 2 cm × 1 cm, was excised. Because the patient was slow to revive after surgery, computed tomography of the head was performed, revealing a large subdural hematoma in the posterior fossa. The patient underwent evacuation of the hematoma in the operating room and was then admitted to the neurologic intensive care unit.

On the second day of hospitalization, the endotracheal tube was removed without complications. Mr. Reilly was easily roused and was oriented to person, place, and time. On the third day, he was alert and remained oriented but developed new dysphagia and dysarthria. A swallowing study documented that he lacked a gag reflex and had difficulty clearing secretions. Because the risk for aspiration was high, he was given nothing by mouth and a Dobbhoff feeding tube was ordered. At this time, the Foley catheter and the arterial catheter were removed; one peripheral intravenous catheter remained. After removal of the Foley catheter, the patient was unable to void. A straight urinary catheter was inserted, and 700 mL of clear yellow urine was removed. The patient required another straight urinary catheterization 4 hours later, and 500 mL of urine was removed. Thereafter, the patient was able to void into a urinal without difficulty. Other than the preoperative dose of vancomycin, the patient did not receive antibiotics.

RISKS FOR INFECTIOUS COMPLICATIONS DURING HOSPITALIZATION

This elderly patient with noncurable metastatic lung cancer underwent a palliative intracranial surgical procedure requiring postoperative intensive care. Even with flawless care, he was prone to developing serious infectious complications as a consequence of both endogenous risk factors (those that were intrinsic to his underlying health status) and exogenous risk factors (those that were attributable to the structure and processes of his complex medical care).

Data from the National Nosocomial Infections Surveillance (NNIS) System of the U.S. Centers for Disease Control and Prevention (CDC) provide an aggregate view of the frequency of common infections among hospitalized patients in the United States (**Table**) (1, 2). Infection incidence rates are presented as device-specific incidence densities (number of infections per device-days × 1000) to adjust for the two most powerful predictors of infection risk: length of hospital stay and use of invasive devices.

Urinary tract infections are the most common hospital-onset infections; they account for approximately 40% of such infections in the United States (3, 4). More than 80% of urinary tract infections are associated with an indwelling urinary catheter, and risk increases with duration of catheterization. Mr. Reilly was at risk for urinary tract infection because he was elderly, had a history of malignancy, and had had a urinary catheter in place for more

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*This paper was prepared by Julie Louise Gerberding, MD, MPH, for the Quality Grand Rounds series. Sanjay Saint, MD, MPH, and Kaveh Shojania, MD, prepared the case for presentation.

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Table. **Incidence of Infection in the Intensive Care Unit from January 1995 to April 2000, according to the National Nosocomial Infections Surveillance System**

Type of Intensive Care Unit	Type of Infection	Pooled Mean Infection Incidence Density*
Medical	Ventilator-associated pneumonia	6.4
	Catheter-associated urinary tract infection	5.9
	Vascular catheter–associated bloodstream infection	5.3
Surgical	Ventilator-associated pneumonia	12.1
	Catheter-associated urinary tract infection	4.3
	Vascular catheter–associated bloodstream infection	4.9

* Pooled mean infection incidence density = number of infections per device-days × 1000.

than 24 hours (5). He was also at increased risk for catheter-related urinary tract infection because he did not receive systemic antibiotics effective against gram-negative bacilli (5–7). However, administration of prophylactic antibiotics solely to reduce the risk for catheter-related urinary tract infection is not currently recommended for most hospitalized patients (8).

Pneumonia, the second most common hospital-onset infection, is associated with high mortality rates, increased length of stay, and increased resource utilization (9–11). Pneumonia was recently found to be the leading cause of nosocomial infection in medical–surgical intensive care units, accounting for 31% of all hospital-onset infections (1). Mr. Reilly had at least five endogenous risk factors for pneumonia (chronic pulmonary disease, severe underlying illness, older age, impaired airway reflexes, and male sex) (11–14) and at least two major exogenous risk factors (mechanical ventilation and nasoenteric intubation). Nasoenteric intubation is particularly hazardous in patients with impaired airway reflexes (11–14). Several strategies to decrease pneumonia rates in such patients have been investigated. Nasotranspyloric intubation (that is, advancing the feeding tube into the small intestine) has no clear-cut advantage compared with nasogastric intubation in preventing aspiration or other adverse events (15–17). Some evidence favors the use of enterostomy (gastrostomy or jejunostomy) to reduce aspiration risk, especially when neurologic recovery is unlikely, but the overall protective effect is small (18–21). Proper placement and management of the feeding tube is a more important issue in preventing aspiration. Tube misplacement, tube displacement, unrecognized ileus, gastric distension, and supine patient positioning commonly contribute to hospital-onset aspiration pneumonia (13, 14, 22).

Vascular catheter–related bloodstream infections are less common than urinary tract infections or pneumonia but greatly affect outcomes and costs of care (23, 24). Endogenous risk factors that might have increased Mr. Reilly's risk for vascular catheter–related infection include his age and the severity of his underlying illness. Mr. Reilly had at least one intravascular catheter in place during his entire hospitalization, increasing the risk for vascular catheter–related infection. The risk was minimized, however, because he received peripheral (rather than central) venous and arterial vascular catheters (25). Other common exogenous risk factors, such as errors in intravascular catheter insertion and management and low nurse-to-patient ratio, were not documented in this case (26).

Surgical site infections are uncommon after neurosurgery (27), especially if intraoperative antimicrobial prophylaxis for staphylococcal infection is provided (28, 29). The current infection rate after craniotomy, according to the NNIS System, is approximately 1 surgical site infection per 100 surgeries for patients without special risk factors. This rate doubles for patients with risk factors, including a contaminated, dirty, or infected wound; prolonged surgery; or a preoperative risk class greater than II, according to American Society of Anesthesiologists criteria (27). Mr. Reilly had a preoperative risk class of IV, increasing his infection risk (27).

In summary, Mr. Reilly was at high risk for device-associated and procedure-associated hospital-onset infections. Implementation of evidence-based interventions aimed at prevention should have been a high priority throughout his hospitalization.

CHRONOLOGY OF EVENTS, *CONTINUED*

On the fourth day of hospitalization, the previously ordered Dobbhoff feeding tube was inserted and enteral nutrition was provided. Mr. Reilly received nothing by mouth. He was alert and able to sit upright in a chair. The next day, he was afebrile and neurologically stable but continued to have dysphagia and dysarthria. He was transferred from the intensive care unit to a regular ward.

On the sixth day of hospitalization, Mr. Reilly developed a temperature of 38 °C despite receiving 6 mg of dexamethasone intravenously every 6 hours after surgery. He was also noted to have increased upper airway secretions. Aggressive clearance of pulmonary secretions was requested because the surgical team believed that the low-grade fever was probably due to postoperative atelectasis or an acute exacerbation of chronic bronchitis. Chest radiography and urinalysis were ordered, but several hours elapsed before they were performed, and the physicians did not review the results until the next day. Urine and blood cultures were also ordered. Empirical antimicrobial treatment was not prescribed, and the patient was not evaluated for possible pulmonary embolism.

On the seventh day of hospitalization, Mr. Reilly's temperature was 39.2 °C. His heart rate was 120 beats/min, his blood pressure was 115/53 mm Hg, and his respiratory rate was 30 breaths/min. Arterial blood oxygen saturation was 96% on 4 L of supplemental oxygen delivered by nasal canula. The urinalysis and chest radiograph obtained the previous day *were reviewed, and the results were found to be abnormal. The urinalysis revealed 25 to 50 leukocytes per high-power field and many bacteria. The chest radiograph showed consolidations in the right upper lobe and both lower lobes* (**Figure**). *A sputum Gram stain revealed a moderate number of polymorphonuclear leukocytes; no organisms were noted. The urine and blood cultures obtained on the previous day grew gram-negative bacilli; final identification was pending. Intravenous piperacillin and gentamicin were administered.*

DELAYED INITIATION OF ANTIMICROBIAL THERAPY

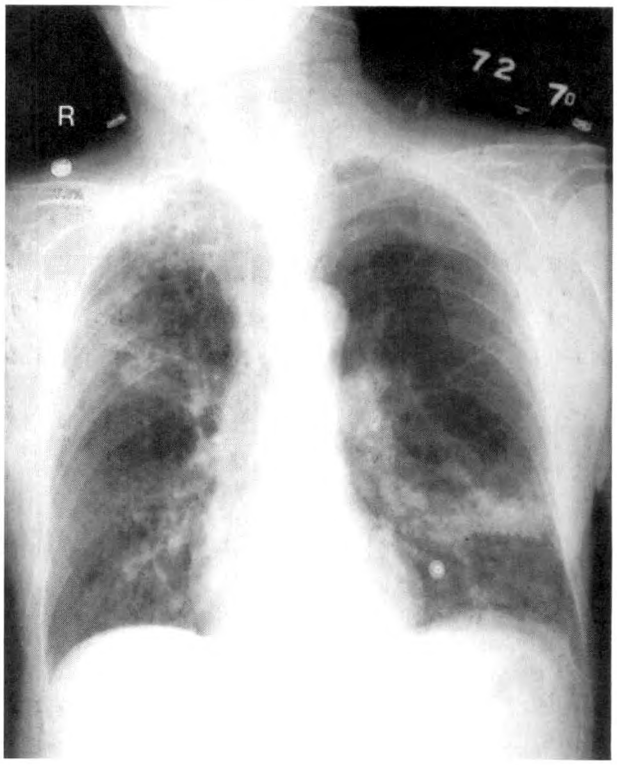
Mr. Reilly developed clinical, microbiological, and radiographic evidence of infection on the sixth day of hospitalization but did not begin receiving antimicrobial therapy for 24 hours. Given his increased risk for pneumonia and urinary tract infection, the failure to start antimicrobial therapy when fever was first noted seems to be an error of omission (30), especially because he was receiving dexamethasone therapy (31, 32). The team caring for Mr. Reilly probably underestimated the importance of low-grade fever in a patient receiving systemic corticosteroids.

Prompt initiation of appropriate antimicrobial therapy improves survival and decreases length of stay in patients with bacteremia (33, 34). All institutions could benefit from a careful internal review of how hospital-onset infections are managed. If treatment delays are common, the institution should seek to improve the systems of care, not simply individual clinicians' responses to suspected infection. Inquiries might be made about the sequence of events after fevers are noted, including time elapsed until patients are evaluated, when tests are ordered, when they are performed, when results become available, and when results are communicated and acted on. Communication networks could also be evaluated to ensure that no barriers obstruct the timely flow of information from one person or service to another. Factors such as inadequate staffing, competing priorities, and fatigue should also be considered.

CHRONOLOGY OF EVENTS, *CONTINUED*

On the eighth day of hospitalization, Mr. Reilly had a temperature of 39.7 °C. His heart rate was 140 beats/min, his respiratory rate was 40 breaths/min, and his blood pressure was 125/88 mm Hg. Arterial blood oxygen saturation was 85% on 4 L of supplemental oxygen delivered by nasal canula. He was transferred to the medical intensive care unit. A chest radiograph again revealed consolidations in the right upper lobe and both lower lobes consistent with pneumonia that had worsened compared with the previous radiograph. The blood culture drawn on the sixth day of hospitalization was growing Klebsiella oxytoca, *and the urine culture was growing* K. oxytoca *and* Escherichia coli. *A sputum culture obtained on the seventh day of hospitalization grew two species of* Pseudomonas aeruginosa. *The patient's antimicrobial therapy was changed to clindamycin, ceftazidime, and gentamicin to cover hospital-onset urinary tract infection and pneumonia.*

Figure. **Chest radiograph obtained on the sixth day of hospitalization.**



On the ninth day of hospitalization, Mr. Reilly was intubated to improve his oxygenation. A rapid taper of dexamethasone was initiated. One blood culture drawn on the seventh day of hospitalization grew coagulase-negative staphylococci. Because of persistent fever, vancomycin was added. Nevertheless, the patient's fever and respiratory failure continued over the next few days. On the 14th day of hospitalization, Mr. Reilly's family requested that he receive comfort care only. His endotracheal tube was removed, and he was discharged to home hospice. He died soon afterward.

ARE NOSOCOMIAL INFECTIONS MEDICAL ERRORS?

This patient, who had an underlying and ultimately fatal metastatic malignancy, underwent a palliative neurosurgical procedure and developed two serious infections that resulted in death. Did these infections and their outcome reflect deficiencies in the quality of health care Mr. Reilly received? Were they a consequence of medical errors (and therefore preventable), or were they unfortunate but unavoidable complications of tertiary care for this severely ill patient?

The answers to these questions are far from clear. Although some interventions may have reduced Mr. Reilly's risk for infection, it is also possible that his course would not have been substantially altered despite the initiation of evidence-based guidelines. Nevertheless, it is important to monitor the incidence of nosocomial infections in health care settings in an attempt to minimize their occurrence.

Rates of hospital-onset infection have been measured for more than 30 years. The NNIS System and similar infection monitoring systems compare the observed infection rate in a given hospital with the aggregate rate observed in a cohort of similar facilities. The NNIS System currently reports "benchmark" (that is, comparison) hospital-onset infection rates based on the experience of more than 300 hospitals that use standardized and validated methods to voluntarily and confidentially report infections to the CDC. In theory, hospitals whose infection rates compare poorly with NNIS benchmarks should be motivated to identify preventable causes of infection and target interventions to prevent systematic errors, unless other explanations for the increased rate are evident. The 30% to 40% decline in infection rates reported by NNIS System hospitals in the past decade suggests that this monitoring and benchmarking approach can be effective in promoting patient safety and preventing some medical errors (2).

Data from the NNIS System have generally been used to motivate institutions with higher-than-expected infection rates to strive for the relevant national benchmark rate. With this approach, the preventability of infections acquired by individual patients has not been routinely assessed unless the institution's overall rates are high or increasing. This monitoring and benchmarking approach is most useful when achieving a "zero rate" is not a realistic expectation or when the preventable fraction of infections (that is, the fraction due to medical errors) is unknown. The result may be both an underestimation of the preventable fraction and missed opportunities to discover new prevention strategies. Unless all institutions continuously strive to reduce their infection rates, there may be little motivation for better-than-average performers to improve, a situation that could lead to a "culture of complacency." A continuous quality improvement model, in which institutions practice an ongoing cycle of event tracking and process improvement, is recommended for infection control activities (2) and has also been applied in some hospitals seeking to reduce serious medication errors (35, 36). A mindset that the current error rate can always be decreased almost certainly explains the fact that other complex industries routinely achieve error rates far below equivalent benchmarks in health care (37). A more aggressive approach to NNIS-type data would prompt institutions with already successful infection control programs to strive for rates even further below current benchmarks, while underperforming institutions would be encouraged to incorporate proven strategies to reach the comparison or benchmark rate. This approach may yield more robust reductions in infection rates than those achieved by our present focus on "underperforming" institutions.

The recent Institute of Medicine report (38) highlighting the relationship among medical errors, adverse events, and health care quality has encouraged new approaches to patient safety and infection prevention. Altering the premise that "many infections are inevitable, although some can be prevented" to "each infection is potentially preventable unless proven otherwise" is consistent with the expectations of patients and the Institute of Medicine. Perhaps hospital-onset infections that cause or contribute to death or other serious adverse consequences should serve as red flags that trigger close scrutiny of the safety and appropriateness of medical treatment, regardless of the institution's overall infection rates.

In addition, although it is not practical or even useful to perform a root-cause analysis of every hospital-onset infection, the local infection control team or other appropriate hospital personnel should review infections that cause substantial harm or are implicated as an attributable cause of death. When preventable causes are suspected, a root-cause analysis to identify factors inherent in the system or processes of care that contributed to the errors should be considered. The analysis starts with an event (for example, urinary catheter–associated sepsis) and progressively moves the focus of evaluation from special causes in clinical processes (for example, use of aseptic technique during catheter insertion) to common causes in organizational processes (for example, reduced staffing ratios) to identify potential interventions for prevention.

Evaluating errors that cause serious adverse events and sentinel events requires time, skill, and tact on the part of the infection control team, quality management staff, and other health care personnel. No data as yet demonstrate that root-cause analysis improves on results attributed to traditional benchmarking and infection control methods. Nevertheless, careful evaluation of the factors contributing to fatal infections and similar adverse events may lead to important systems changes and improved patient safety.

As one element in such a review, it is reasonable to ask whether an anti-infective urinary catheter would have made a difference in preventing Mr. Reilly's septicemia. Several types of anti-infective catheters are available; the best studied are urinary catheters coated with silver alloy, although catheters coated with minocycline–rifampin are also available (39). A meta-analysis of eight trials found a significant reduction in bacteriuria rates in patients given silver alloy catheters compared with standard catheters (40), and this finding has been duplicated in more recent studies (41, 42). The effect of the catheters on reducing more important outcomes, such as septicemia and death, is unclear. However, recent studies suggest that patients such as Mr. Reilly, who have indwelling urinary catheters for 2 to 10 days, are likely to derive both clinical and economic benefits from the silver alloy catheter (40, 43, 44).

WHAT CAN PATIENT SAFETY AND INFECTION CONTROL EFFORTS DRAW FROM EACH OTHER?

Modern patient safety practices, such as root-cause analyses and continuous quality improvement, can enhance the field of infection control. The patient safety movement can also learn much from the traditions of infection control and hospital epidemiology. Precise and valid definitions of infection-related adverse events, standardized methods for detecting and reporting events, confidentiality protections, appropriate rate adjustments for institutional and case-mix differences, and evidence-based intervention programs come to mind. Perhaps most important, reliance on skilled professionals to promote ongoing improvements in care has contributed to the 30-year track record of success in infection prevention and control.

Analogously, in approaching patient safety, standard definitions should be used as much as possible when discussing adverse events and preventability. Health care organizations should be encouraged to pool data on adverse events in a central repository to permit benchmarking, and such data should be appropriately adjusted and reported. Finally, institutions should consider hiring dedicated, trained patient safety officers (comparable to infection control practitioners), as has been done in many Veterans Affairs hospitals (45).

THE INSTITUTIONAL RESPONSE

The institution's infection control committee implemented several strategies to prevent catheter-associated urinary tract infections. First, after reviewing data showing that catheters are inappropriately used in approximately one third of patients (46, 47), that approximately 50% of catheter days are not medically necessary (47), and that attending physicians are unaware of catheter use in approximately 40% of cases (48), the hospital instituted a pilot program of urinary catheter stop orders. In addition, silver alloy urinary catheters are being used in targeted high-risk areas and patients. Although silver alloy catheters cost approximately $5 more per unit, they may be cost-effective in patients who are at high risk for urinary tract infection and require catheterization for at least 2 days (43). Use of these catheters will at first be limited to patients in the intensive care units and on the hematology–oncology wards. The hospital will perform a before-and-after evaluation to assess effectiveness.

The hospital's infection control committee began an intensive educational program highlighting prevention of nosocomial pneumonia, especially in ventilated patients. On the basis of the evidence (49), directives included elevation of the head of the bed, strict adherence to hand washing before and after contact with patients, aseptic management of endotracheal tubes, and extubation as soon as possible.

CONCLUSIONS

The institution should be commended for taking action. Systematic examination of events, relevant processes of care, and prevention options is an excellent contemporary model for preventing infections and promoting patient safety. Nevertheless, a before-and-after evaluation in a single hospital will not usually have adequate statistical power to detect a meaningful difference. When a difference is detected, secular changes may be contributory. We need large, multicenter studies to assess novel strategies for patient safety enhancement.

From the Office of the Director, Centers for Disease Control and Prevention, Atlanta, Georgia.

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Excerpts of the question-and-answer session and excerpts of an interview with the chair of the institution's infection control committee are available at www.annals.org.

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2002–2003 Series: Update Sessions from ACP–ASIM's 2002 Annual Session
David A. Cramer, MD, and Paul T. Kefalides, MD, Co-Editors

UPDATE

Update in Psychiatry

Robert K. Schneider, MD, and James L. Levenson, MD

This is the third Update in Psychiatry since 1999 (1, 2). Combined with the Update in Addiction Medicine (3), these Updates represent a growing source of evidence-based information on psychiatry for general internists. This Update is broadly divided into the following categories: mood disorders, anxiety disorders, medical–psychiatric comorbid conditions, and cognitive disorders.

Mood (Affective) Disorders

Which Selective Serotonin Reuptake Inhibitor Works Best?

Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA. 2001;286:2947-55. [PMID: 11743835]

Selective serotonin reuptake inhibitors (SSRIs) are the most common class of antidepressants prescribed by primary care physicians in the United States. Despite the claims of pharmaceutical companies, it is not known whether one SSRI is more effective than another in the treatment of major depression.

Kroenke and colleagues conducted a randomized trial to compare the effectiveness of paroxetine ($n = 189$), fluoxetine ($n = 193$), and sertraline ($n = 191$) in patients whose primary care physician believed they should have antidepressant therapy for depression. The patients were enrolled from two large primary care research consortiums.

No statistical differences arose among the three SSRIs for any outcome measured. The percentage of patients who met diagnostic criteria for major depression decreased from 74% at baseline to 32% at 3 months and 26% at 9 months. Recovery rates did not differ among the three SSRIs: paroxetine, 81%; fluoxetine, 77%; and sertraline, 84%. The three groups contained similar percentages of patients who continued therapy with their initially assigned SSRI for 9 months: paroxetine, 41%; fluoxetine, 50%; and sertraline, 43%.

Nonpsychiatrists prescribe more than 75% of the SSRIs in the United States. Although trials have compared two SSRIs, no large-scale clinical trials have compared the three most frequently prescribed SSRIs. This study demonstrates equal effectiveness for treatment of depression among these three SSRIs used in a primary care setting for 9 months. However, the study had a few limitations. It contained too few patients to allow detection of subtle differences in agents, and the patients were selected on the basis of the primary physicians' perceived need for treatment rather than because they met diagnostic criteria for major depression. The latter limitation may skew the outcomes by allowing inclusion of patients with minor depression or another psychiatric illness. In addition, the study lacked placebo control; thus, it could be argued that the three drugs were equivalent because they all had nonspecific effects that would be indistinguishable from those caused by placebo. These limitations would not be expected to favor any one of the medications.

This study shows that paroxetine, fluoxetine, and sertraline do not differ when used in a primary care setting. When choosing an SSRI, clinicians should not consider differences in efficacy, despite the claims of pharmaceutical representatives.

Which Came First, Erectile Dysfunction or Depressive Symptoms?

Seidman SN, Roose SP, Menza MA, et al. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry. 2001;158:1623-30. [PMID: 11578994]

Depression and erectile dysfunction often occur together in men, but the causal relationship is unclear. Seidman and colleagues evaluated the effects of sildenafil among men with erectile dysfunction and mild-to-moderate depressive symptoms in a randomized, double-blind, placebo-controlled, flexible-dose (25 to 100 mg) trial over 12 weeks. Patients had only mild depression; those meeting criteria for major depression were excluded.

Erectile dysfunction, orgasmic function, sexual desire, and overall satisfaction with intercourse improved significantly more in the sildenafil group ($P < 0.001$ for all comparisons). Patients who responded to treatment (48 of 66 patients given sildenafil and 10 of 70 given placebo) had significant improvements in depression symptoms and quality of life compared with nonresponders. The results may not be generalizable to patients with major depression or those taking psychotropic medications, who were excluded. This 12-week trial was too brief to allow evaluation of the effects of long-term use. However, in men with minor depression and erectile dysfunction, sildenafil was associated with improvement in depressive symptoms. When erectile function improved, so did mood. This finding is consistent with the experience seen with treatment of specific symptoms of minor depression (for example, insomnia and mild anxiety).

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Is St. John's Wort an Effective Antidepressant?

Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St John's wort in major depression: a randomized controlled trial. JAMA. 2001;285:1978-86. [PMID: 11308434]

While almost 30 controlled trials have concluded that St. John's wort (*Hypericum perforatum*) is effective for treating depression, methodologic criticism has undermined confidence in their results. Shelton and colleagues compared the efficacy and safety of St. John's wort with those of placebo in a randomized, double-blind clinical trial in adult outpatients with major depression at 11 academic medical centers in the United States. A 1-week, single-blind run-in placebo phase was used to exclude patients with early response to placebo. Two hundred patients received either St. John's wort (900 to 1200 mg/d; $n = 98$) or placebo ($n = 102$) for 8 weeks.

No outcome measures significantly differed between the two groups, although depression improved over time in both. More patients reached remission with St. John's wort, but the rates were very low (14.3% vs. 4.9% in the placebo group; $P = 0.02$). St. John's wort was safe and well tolerated; only 1% of patients discontinued use because of adverse effects. Headache was the only symptom more common with St. John's wort than with placebo (41% [95% CI, 30.5% to 49.9%] vs. 25% [CI, 17.0% to 33.9%]).

In this study, St. John's wort was ineffective for treatment of major depression. The participants had chronic depression (average duration, >2 years) of at least moderate severity and were recruited from tertiary care clinics. Thus, the results may not be generalizable to patients with less severe depression in community settings.

Many patients ask their physicians about St. John's wort (and other herbal preparations) and may have already taken it. Physicians should advise them that St. John's wort may not be effective and is not a substitute for treatments with demonstrated efficacy for more severe major depression (antidepressants and psychotherapy). While St. John's wort is safe when taken alone, significant adverse drug interactions have occurred with warfarin, cyclosporine, theophylline, digoxin, protease inhibitors, anticonvulsant agents, oral contraceptives, triptans, and SSRIs (4, 5).

Is Estrogen an Antidepressant in Menopausal Women?

Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry. 2001;58:529-34. [PMID: 11386980]

Depressive symptoms and somatic symptoms are common in women entering menopause. Studies of estrogen replacement for mood symptoms have shown mixed results. Issues involving estrogen preparation, endocrinologic confirmation of perimenopause, measurement of mood symptoms, and loss of blinding to treatment assignment because of uterine bleeding have limited previous studies.

Soares and colleagues sought to determine the efficacy of estrogen replacement treatment for mood symptoms in depressive disorders among women in endocrinologically confirmed perimenopause. They conducted a randomized, double-blind, placebo-controlled trial of women who had follicle-stimulating hormone levels greater than 25 IU/L and met diagnostic criteria for a major depressive disorder (major depression, dysthymia, or minor depression). Patients received 100 μg of 17β-estradiol given through transdermal patches ($n = 25$) or placebo ($n = 25$) for 12 weeks. The patients were reevaluated after a 4-week washout period at the conclusion of the study.

Estradiol levels were significantly higher than baseline in the treatment group ($P < 0.001$) but not the placebo group. Depressive symptoms, assessed by the Montgomery–Åsberg Depression rating scale, resolved in 68% of patients treated with estradiol and 20% of placebo recipients ($P = 0.001$). Responses did not differ according to type of depressive disorder. Menopausal symptoms, assessed by the Blatt–Kupperman Menopausal Index, were reduced by 50% in 68% of patients treated with estradiol and 28% of those receiving placebo ($P = 0.005$). After the washout period at the end of estradiol treatment, 59% of women in the estradiol group but none of the women in the placebo group were still in remission from depression. After the washout period, the treatment group showed a significant increase ($P < 0.001$) in menopausal symptoms but the placebo group did not.

In this study, transdermal estrogen patches were effective treatment for depressive symptoms in some perimenopausal women. The patients were recruited from a specialized outpatient clinic, which may affect the generalizability of the results. In addition, 12 weeks is a relatively short period within which to expect full response from treatment, and 4 weeks is a short period for assessing relapse of depression. Similarly, physicians should be cautious about prescribing estrogen for treatment of depression, especially in view of the adverse effects of estrogen on cardiovascular outcomes and breast cancer incidence in the Women's Health Initiative trial (6).

This study is part of a growing body of evidence indicating that estrogen influences central nervous system functions. In previous placebo-controlled studies of estrogen replacement, oral estrogen preparations did not significantly affect mood. Soares and colleagues suggest that transdermal estrogen provides a faster increase and steadier level of serum estradiol than do oral preparations. This may be important in the treatment of depression associated with perimenopause.

How Often Do Depressed Patients Turn Out To Have Bipolar Disorder?

Goldberg JF, Harrow M, Whiteside JE. Risk for bipolar illness in patients initially hospitalized for unipolar depression. Am J Psychiatry. 2001;158:1265-70. [PMID: 11481161]

Both psychiatrists and nonpsychiatrists fail to diagnose bipolar disorder in a substantial proportion of depressed patients. Correct diagnosis is important because the prescription of antidepressants without mood stabilizers may precipitate a switch to mania. How often will patients presenting with depression turn out to really have bipolar disorder? Few long-term studies have measured rates of conversion from unipolar to bipolar depression. The rates vary across subpopulations of depression. One study (7) found that up to 20% of outpatients with depression had new-onset bipolar disorder. In depressed adolescents, the conversion rate has varied from 19% to 37%.

Goldberg and colleagues prospectively followed a cohort of young people for 15 years to identify clinical features that predict subsequent mania or hypomania. They also studied the effect of antidepressants on the induction of mania or hypomania.

The cohort consisted of 74 patients (mean age, 23 years) hospitalized for unipolar depression. After 15 years of follow-up, 41% of patients had developed either hypomania or mania (hypomania, 26%; mania, 15%). Eight of the 10 patients with psychotic depression developed hypomania or mania. In contrast, 34% of the nonpsychotically depressed patients eventually became manic or hypomanic ($P = 0.003$). Conversion to bipolar illness occurred at the same rate whether or not the patient took antidepressants.

This study suggests that younger patients who have unipolar depression with psychotic features may be at a particularly high risk for conversion to bipolar depression. Major depressive disorders are the most common psychiatric disorders seen in primary care, yet physicians seldom obtain a history of mania and hypomania or use mood stabilizers to treat these patients. General internists should screen for mania (and hypomania) in all patients who are suspected of having major depression, especially if they plan to prescribe an antidepressant.

How Good Is the Care Given for Depressive and Anxiety Disorders?

Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry. 2001;58:55-61. [PMID: 11146758]

Depressive and anxiety disorders are common and cause substantial disability. Medications and psychotherapies are effective, but many patients do not receive adequate treatment. Young and colleagues reviewed data from the National Comorbidity Survey (1997–1998) to estimate the rate of appropriate treatment of anxiety and depressive disorders in the U.S. population, along with the effects of insurance, provider type, and demographic characteristics.

During a 1-year period, 83% (CI, 81% to 85%) of 1636 adults with a depressive or anxiety disorder saw a health care provider, and 30% (CI, 28% to 33%) received appropriate treatment. Most saw only their primary care physician, and 19% (CI, 16% to 23%) of those patients received appropriate care. Ninety percent (CI, 85% to 94%) of the 320 patients who saw a mental health professional received appropriate care. Insurance status affected whether the individual saw a provider but had no effect on appropriateness of care. Appropriate treatment was less likely for men, black persons, less educated persons, and those younger than 30 or older than 59 years of age. When psychiatric medications were used, the dose and duration of therapy were appropriate for about 75% of the patients. Among patients seeing primary care physicians, those who received poor-quality care were less likely to report that their mental health problems were evaluated (35.6% vs. 65.3%; $P < 0.001$), that psychiatric drugs were recommended (11.4% vs. 55.7%; $P < 0.001$), or that referral to a mental health specialist was made (4.1% vs. 23.5%; $P < 0.001$) compared with those who received appropriate care. Patients who received poor-quality care were less likely than patients who had appropriate care to view themselves as needing mental health care (31.4% vs. 70%; $P < 0.001$).

These results indicate that most adults in the community with depressive or anxiety disorders do not receive appropriate treatment, even though the great majority did see a health care professional. In the past, most patients with depressive disorders treated in primary care settings did not receive adequate doses of medication for an adequate duration. This more recent study shows that prescribed psychiatric medications were usually given at an appropriate dose and duration. Thus, the current barriers to appropriate treatment of depression and anxiety disorders lie in recognition, diagnosis, referral, and acceptance by patients.

Anxiety Disorders

What Are the Psychiatric Consequences of a Terrorist Disaster?

North CS, Nixon SJ, Shariat S, et al. Psychiatric disorders among survivors of the Oklahoma City bombing. JAMA. 1999;282:755-62. [PMID: 10463711]

According to North and colleagues, before the September 11th attacks, the bombing of the Alfred P. Murrah Federal Building in Oklahoma City, Oklahoma, was the "most severe incident of terrorism ever experienced on American soil." Survivors are concerned about their response to such events, and physicians should understand post-traumatic reactions and learn to distinguish effective coping strategies and normal reactions from maladaptive responses and psychiatric illness.

North and colleagues assessed the psychiatric impact of the Oklahoma City bombing on adult survivors directly exposed to the bomb blast. The authors paid particular attention to post-traumatic stress disorder (PTSD), psychiatric comorbidity, and predictors of postdisaster psychopathology.

Of the 182 people interviewed, 87% reported injuries (77% of the 182 required medical treatment). The most common postdisaster disorders were PTSD and major depression. Seventy-four percent of patients with postdisaster PTSD and 56% of those with postdisaster major depression had not experienced these disorders before the bombing. Conversely, 71% of patients with no psychiatric diagnosis before the disaster remained without a diagnosis afterward. More than 80% of the survivors experienced either intrusive reexperiences or hyperarousal (two of the three criteria for PTSD), while only 34% of survivors met all three PTSD criteria. In this study sample, the combination of avoidance and numbing (the third criterion for PTSD) was 100% sensitive for detecting PTSD.

As with all retrospective analyses, recall bias in this study is possible. The participants were survivors directly exposed to the blast, not a sample of the general population who had knowledge of the blast. This limits generalizability of the study findings to the general population.

This study helps us understand potential psychiatric consequences of terrorism, with PTSD and major depression at the top of the list. Although more than 80% of the participants had symptoms of hyperarousability or reexperiencing of the trauma, only 34% ultimately met criteria for PTSD. Most patients without a predisaster psychiatric diagnosis did not have a postdisaster psychiatric diagnosis. These data offer reassurance that most people without psychiatric problems before a disaster will not develop one after the disaster. They also suggest that it is part of "normal" experience to have hyperarousability or to reexperience the trauma immediately after a traumatic event.

As reported in our 1999 Update (1), it is important to remember that the sudden unexpected death of a loved one is the most common trauma that the general population experiences. It carries a conditional risk for PTSD of 14.3% (8), compared with the 34% seen in persons who survived the Oklahoma City bombing. Lack of social support and continued life stressors after the trauma are more predictive of subsequent PTSD than are pretrauma risk factors (for example, sex and history of trauma) (9). However, for symptoms that persist and meet criteria for full PTSD, effective pharmacotherapy and psychotherapy are available.

What Is the Best Initial Drug Treatment for Panic Disorder?

Goddard AW, Brouette T, Almai A, et al. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry. 2001;58:681-6. [PMID: 11448376]

The SSRIs are indicated in the treatment of all the anxiety disorders, including panic. However, the response to SSRIs is delayed (4 to 12 weeks for maximum effect), and early side effects are frequent. For these reasons, patients with anxiety disorders frequently discontinue SSRI treatment prematurely before benefiting from the medication. Many psychiatrists use early coadministration of benzodiazepines with SSRIs to treat panic disorder and other anxiety disorders. A short-acting benzodiazepine such as alprazolam seems like a good choice because of its rapid onset of action. However, this drug can provoke a rebound in anxiety symptoms between doses and when the drug dose is being tapered. Clonazepam is an intermediate–half-life benzodiazepine with a slower onset of action than alprazolam. When combined with an SSRI, it provides the early symptom reduction seen with alprazolam, but it is not as difficult to taper after the SSRI has taken effect.

Goddard and colleagues performed a 12-week, randomized, double-blind, placebo-controlled trial to test the efficacy of early coadministration of clonazepam and sertraline for treating panic disorder in adults. Patients received open-label sertraline to a target dose of 100 mg and blinded treatment with either clonazepam, 0.5 mg ($n = 22$), or placebo ($n = 25$) three times daily. Beginning at week 4 and continuing for the next 3 weeks, the clonazepam dose was tapered.

Relief of panic symptoms was significantly different at week 1 (41% for clonazepam vs. 4% for placebo; $P = 0.003$) and week 3 (63% vs. 32%; $P = 0.05$). The response rates did not significantly differ at other times (that is, during and after tapering of the clonazepam dose). At the end of the trial, the response rates of both groups exceeded 70%. Secondary measures (dropout rates, adverse reactions) did not differ between groups.

Symptoms of panic disorder can rapidly stabilize with the coadministration of clonazepam and sertraline. This effect is maintained through the tapering and discontinuation of clonazepam therapy. The small size of the study could explain the lack of expected differences in secondary measures and may limit generalizability. In clinical practice, the SSRI dose may be titrated up more slowly and the target dose can be lower, or the dose can be titrated for a longer period to a higher level. In either case, the time before stabilization of the SSRI dose would be longer, thereby potentially increasing the value of the early symptom reduction achieved by coadministration of clonazepam. However, Goddard and colleagues' study shows the advantage of a treatment strategy that internists can use in the early treatment of panic disorder.

Medical–Psychiatric Comorbid Conditions

Can Medication-Induced Depression Be Prevented?

Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med. 2001;344:961-6. [PMID: 11274622]

Depression, often resulting in suicidal ideation, is the most frequent adverse effect leading to discontinuation of interferon therapy. Yet interferon is important in the treatment of hepatitis C, multiple sclerosis, and cancer. Antidepressants have been reported to be effective in treating interferon-induced depression.

To determine whether pretreatment with antidepressants would reduce depressive symptoms after interferon-α treatment, Musselman and colleagues performed a randomized, double-blind, placebo-controlled trial. Paroxetine ($n = 20$) or placebo ($n = 20$) was given to patients 2 weeks before initiation of high-dose interferon-α therapy for malignant melanoma and was continued for 12 weeks.

Major depression developed in 11% of the paroxetine group and 45% of the placebo group (relative risk, 0.24 [CI, 0.08 to 0.93]). Severe depression led to discontinuation of interferon-α therapy in 5% of the paroxetine group and 35% of the placebo group (relative risk, 0.14 [CI, 0.05 to 0.85]). Interferon-α therapy was stopped in 7 of the 9 patients (78%) in the placebo group who developed major depression.

Pretreatment with paroxetine appears to reduce the emergence of depression induced by interferon-α in patients with malignant melanoma. The occurrence of major depression usually results in discontinuation of therapy with interferon-α, but this study shows that antidepressant treatment is a valuable tool for facilitating interferon-α therapy.

Results may not be generalizable to interferon-α treatment of other diseases, such as hepatitis C, or to other interferons, such as interferon-β. In addition, this study used pretreatment therapy for depression; the results could differ if the antidepressant is given after symptoms of depression have already appeared.

Depression can be a serious side effect of many drugs, including corticosteroids, β-blockers, isotretinoin, and interferon. When substituting an alternative medication is not possible, it is appropriate to try treating the drug-induced depression with antidepressants or, in some cases, pretreating before administering the drug.

What Is the Risk for Sudden Death with Antipsychotic Agents?

Ray WA, Meredith S, Thapa PB, et al. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry. 2001;58:1161-7. [PMID: 11735845]

Case reports have linked antipsychotic drugs with prolongation of the corrected QT interval (QT_c), torsade de pointes, and sudden death. "Black box" warnings about these risks have been added to entries in *Physicians' Desk Reference* for the older antipsychotics thioridazine and mesoridazine. A new antipsychotic agent, sertindole, was not registered in the United States because it caused QT_c prolongation and sudden death. To determine the risk for sudden cardiac death in patients receiving antipsychotic medications, Ray and colleagues retrospectively reviewed the cohort study of Medicaid enrollees in Tennessee (481 744 persons with 1 282 996 person-years of follow-up, 1988 to 1993). The authors calculated multivariate rate ratios, adjusting for age, sex, race, cardiovascular disease, and noncardiovascular illness.

The adjusted risk ratios for sudden cardiac death were as follows: use of moderate-dose antipsychotic agent versus nonuse, 2.39 (CI, 1.77 to 3.22); use of low-dose antipsychotic agent versus nonuse, 1.30 (CI, 0.98 to 1.72); use of moderate-dose antipsychotic agent in patients with severe cardiovascular disease versus nonuse, 3.53 (CI, 1.66 to 7.51). There were 1487 sudden unexpected cardiac deaths (11.6 per 10 000 person-years in patients receiving moderate-dose antipsychotic agents and 367 per 10 000 person-years in patients with severe cardiovascular disease).

This study shows relative and absolute increases in risk for sudden death in patients taking moderate doses of antipsychotic agents. The study design does not allow conclusions on causality. The data were obtained before the new "atypical" antipsychotic agents (risperidone, olanzapine, quetiapine, and ziprasidone) became available. The information on risk factors for cardiovascular disease was limited. The authors could not control for information on smoking status and obesity, which are common in patients with chronic serious mental illness, because this information was not available. The authors did control for smoking-related respiratory disease and known coronary artery disease.

Although several antipsychotic agents have been documented to cause torsade de pointes and sudden death, thioridazine carries the biggest risk (10). No association has been found with olanzapine, quetiapine, risperidone, or ziprasidone (although the latter, a new agent, can prolong QT_c). Physicians would be prudent to ask any patient who is to receive antipsychotic medication (or who is already receiving one) about any history of syncope and any family history of unexplained sudden deaths or the prolonged QT syndrome. Patients who have known heart disease or are at high risk for it or those who are receiving other drugs that can prolong QT_c should have electrocardiography before beginning treatment. People with pretreatment prolonged QT_c should undergo periodic electrocardiography and should receive antipsychotic agents that do not prolong QT_c, if possible.

Does Group Therapy Prolong Life in Patients with Metastatic Breast Cancer?

Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med. 2001;345:1719-26. [PMID: 11742045]

Group therapy has been reported to provide benefits for patients with metastatic breast cancer (and other life-threatening illnesses), including improvement in mood, pain control, and, in some studies, survival.

To assess whether supportive-expressive group therapy (in addition to routine care) influences survival, mood, and pain in women with metastatic breast cancer, Goodwin and colleagues conducted a large multicenter, randomized trial in 235 women at seven Canadian cancer centers. Group therapy consisted of weekly 90-minute sessions for at least 1 year.

Women in the intervention group had fewer psychological symptoms and better pain control ($P = 0.04$) than women in the control group. These benefits occurred in women who were more distressed at baseline. Group therapy did not prolong survival compared with routine care alone (mean survival, 17.9 vs. 17.6 months; hazard ratio, 1.06 [CI, 0.78 to 1.45]).

In this study, supportive-expressive group therapy improved mood and perception of pain, particularly in women who were more distressed, but it did not prolong survival. Some baseline disease variables differed between the groups, although these differences did not appear to influence the results. Only about 9% of eligible women were randomly assigned, raising concern about limited generalizability to other women.

Many women with breast cancer ask their health care providers about support groups. Some women are not comfortable with participating in such groups but may feel anxious about forgoing them, especially after exposure to media accounts that such therapy is "proven" to increase survival. Physicians can now tell their patients that the benefits of group therapy lie in improvements in mood and pain. Choosing not to participate will not adversely affect survival.

Cognitive Disorders

Does Cognitive Function Decline after Coronary Artery Bypass Grafting?

Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395-402. [PMID: 11172175]

Previous studies have assessed perioperative cognitive decline after coronary artery bypass grafting (CABG). The incidence of decline appears to be highest at discharge; for most patients, cognition then gradually improves during the ensuing 6 months. However, a substantial number of patients (10% to 30%) have persistent decline in cognitive functioning.

Newman and colleagues prospectively followed cognitive functioning before and after CABG for 5 years. They enrolled 261 patients undergoing elective CABG from 1989 to 1993. Neurocognitive testing was done before surgery; the day of discharge; and at 6 weeks, 6 months, and 5 years after CABG.

The incidence of cognitive decline was 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. Follow-up of patients with and without cognitive decline at discharge showed that most returned to baseline functioning within 6 months. However, at 5 years, patients with cognitive decline at discharge had a marked decline from their baseline functioning ($P < 0.001$) whereas the patients without cognitive decline at discharge did not. This association remained significant even after adjustment for factors such as age and education level. Attrition from the study was significant; only 172 of the original 261 patients were available for long-term follow-up. Patients who did not complete follow-up were more likely to have more complex illness (that is, American Society of Anesthesiologists class IV disease [incapacitating systemic disease that is a constant threat to life], previous myocardial infarction, and history of symptomatic neurologic disease). This selective attrition may underestimate the persistent decline seen in subsequent follow-up visits.

Before elective CABG, physicians should discuss the potential for cognitive decline with patients and their families. Patients with cognitive decline immediately after elective CABG seem to have increased risk for long-term cognitive decline. At this time, one can neither predict who will have cognitive decline nor fully explain the reason for the decline. Thus, it is reasonable to state that cognitive decline can occur and is not infrequent, and that most patients will improve over the first year but that many will have impairment 5 years after surgery. This discussion is less important among patients for whom CABG is intended to prolong life. However, particularly for older patients (whose quality-of-life issues may be more paramount), the balance between relief of pain and the risk for cognitive decline should be carefully considered among patients in whom medical management or angioplasty is not an alternative.

Is There a Quick and Accurate Way To Screen for Dementia?

Scanlan J, Borson S. The Mini-Cog: receiver operating characteristics with expert and naïve raters. Int J Geriatr Psychiatry. 2001;16:216-22. [PMID: 11241728]

Borson S, Scanlan J, Brush M, et al. The mini-cog: a cognitive "vital signs" measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15:1021-7. [PMID: 11113982]

Busy primary care internists do not have time for long screening algorithms to detect mental illness; they need time-efficient case-finding strategies. For example, in screening for mood disorders, asking one question, "Do you feel depressed?", has a sensitivity of approximately

90%. The Mini-Mental Status Examination (MMSE), often used in clinical practice, is hard to remember and time-consuming. The Mini-Cog combines the three-item recall from the MMSE and the Clock Drawing Test. Critchley first described the Clock Drawing Test in 1953. In its current format, the subject tries to fill in the numbers on a predrawn circle and then add the hands for a designated time.

Scanlan and colleagues evaluated the Mini-Cog (three-item recall and Clock Drawing Test) as a case-finding strategy for cognitively impaired adults. A total of 249 community-dwelling persons (173 women and 76 men) were evaluated in a university memory clinic. All participants completed the MMSE, the Cognitive Abilities Screening Instrument (CASI), and the Mini-Cog. Expert raters performed the MMSE and the CASI, which was the diagnostic reference standard, and "naive" raters performed the Mini-Cog. Results were compared between rating instruments and raters.

The Mini-Cog had the highest sensitivity (99%) compared with the CASI (92%) and the MMSE (91%). The CASI had the greatest specificity (96%) compared with the Mini-Cog (93%) and the MMSE (92%). Concordance between naive and trained raters was greater than 98% for normal, moderately impaired, and severely impaired clock drawings. Concordance decreased to 60% in mildly impaired clock drawings, but assuming that inexperienced raters would score mildly impaired clocks as normal had little effect on the sensitivity and specificity of the Mini-Cog (97% and 95%, respectively).

The major limitation of these studies was their study sample—attendees of a memory clinic, who have a greater incidence of dementia than persons in the community.

The Mini-Cog provides an effective, sensitive, and specific first-stage screening tool for detecting dementia. Naive raters performed essentially as well as experts. This evidence supports having a nurse or other health professional administer the Mini-Cog. The clock-face drawing task requires adequate functioning in the temporoparietal and frontal cortical areas, which are commonly affected in dementias but are not fully tested with the MMSE. The combination of the three-item recall with Clock Drawing Test (the Mini-Cog) provides a sensitive, specific, and easily administered alternative to the MMSE. Combining this first-stage screening with a brief second-stage interview with a caregiver appears to be an effective strategy for dementia screening but warrants further population-based testing.

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Breast Cancer in Men

Sharon H. Giordano, MD; Aman U. Buzdar, MD; and Gabriel N. Hortobagyi, MD

Purpose: **Breast cancer in men is uncommon; 1500 new cases are diagnosed in the United States yearly. Optimal management of breast cancer in men is unknown because the rarity of the disease precludes large randomized trials. A review of the literature was undertaken with emphasis on articles published over a 10-year period.**

Data Sources: **Articles published between 1942 and 2000 on breast cancer in men were identified by using CancerLit, MEDLINE, and study bibliographies.**

Study Selection: **All retrospective series and studies focusing on the epidemiology, risk factors, genetics, and pathology of breast cancer in men.**

Data Extraction: **Data on the epidemiology, risk factors, genetics, pathology, molecular markers, prognostic factors, therapy, and outcomes of breast cancer in men.**

Data Synthesis: **Carcinoma of the male breast accounts for 0.8% of all breast cancers. Risk factors include testicular disease, benign breast conditions, age, Jewish ancestry, family history, and the Klinefelter syndrome. *BRCA2* mutations predispose men to breast cancer and may account for 4% to 14% of all cases. Pathology data were reviewed: 81% of tumors were estrogen receptor positive, 74% were progesterone receptor positive, 37% overexpressed c-erbB-2, 30% overexpressed p53, 79% overexpressed Bcl-2, 51% overexpressed cyclin D1, and 39% overexpressed epidermal growth factor receptor. Prognostic factors include tumor size, histologic grade, and lymph node status; survival is similar to that of breast cancer in women when patients are matched for age and stage. Adjuvant hormonal therapy and chemotherapy, using the same guidelines as for women, are recommended for men. Hormonal therapy is the primary therapy for metastatic disease; chemotherapy should be reserved for hormone-refractory disease.**

Conclusion: **Breast cancer is similar in men and women; however, breast cancer in men is more frequently hormone receptor positive and may be more sensitive to hormonal therapy.**

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Carcinoma of the male breast is a relatively rare disease that accounts for less than 1% of all cases of cancer in men. Because of the rarity of the disease, most information has been obtained from small, single-institution, retrospective studies or by extrapolation from breast cancer trials in women. We have previously reviewed the literature on breast cancer in men (1) and now present an update that focuses on the molecular and pathology data that has been published over the past decade.

METHODS

We identified articles published between 1942 and 2000 on breast cancer in men using CancerLit, MEDLINE, and bibliographies from other publications. We reviewed all retrospective series and studies that focused on the epidemiology, risk factors, genetics, pathology, molecular markers, prognostic factors, therapy, and outcomes of breast cancer in men.

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EPIDEMIOLOGY AND RISK FACTORS

In 2002, approximately 1500 new cases of male breast cancer will be diagnosed in the United States, and 400 men will die of this disease (2). In contrast to the increasing incidence of breast cancer in women, the incidence of breast cancer in men has remained stable over the past four decades (3). The median age at diagnosis is 68 years compared with 63 years in women (4); however, the disease has been reported in males ranging from 5 to 93 years of age (5). The bimodal age distribution seen in women is absent in men; the incidence increases exponentially with age (6). In most western countries, men account for approximately 1% of cases of breast cancer. In Tanzania, by contrast, 6% of cases of breast cancer are diagnosed in men (7), and in countries in central Africa, a substantially higher proportion of cases of male breast cancer have been reported (8). The reasons for this geographic variability remain unclear.

Many of the risk factors (**Table 1**) for breast cancer in men involve abnormalities in estrogen and androgen balance, which indicates that breast cancer in men, as in women, may be hormonally driven. An elevated risk has been seen in patients with undescended testes, congenital inguinal hernia, orchiectomy, orchitis, testicular injury, and infertility (8, 9). The Klinefelter syndrome, which is characterized by a 47,XXY karyotype, small testes, azospermia, and gynecomastia, is also a risk factor for breast cancer in men; affected men may have up to a 50-fold increased risk (10). Breast cancer in men may be a marker for the Klinefelter syndrome; between 4% and 20% of men with breast cancer have been unexpectedly found to have this syndrome, which affects only 0.1% of the general population (8, 10, 11). Other possible risk factors that relate to hormonal levels include obesity, which causes increased peripheral aromatization of estrogens, and cirrhosis, which results in a hyperestrogenic state (8, 9, 12, 13).

A family history of breast cancer in female relatives has also been shown to be an important predisposing factor. Data from the Surveillance, Epidemiology, and End Re-

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Table 1. **Risk Factors for Breast Cancer in Men**

- Testicular abnormalities
  - Undescended testes
  - Congenital inguinal hernia
  - Orchiectomy
  - Orchitis
  - Testicular injury
- Infertility
- Klinefelter syndrome
- Positive family history
- Benign breast conditions
  - Nipple discharge
  - Breast cysts
  - Breast trauma
- Radiation exposure
- Increasing age
- Jewish ancestry

sults program of the National Cancer Institute showed that men with a positive family history have an odds ratio for developing breast cancer of 3.98 (14). The risk increases with increasing numbers of first-degree relatives affected and with young age at diagnosis in affected relatives. Benign breast conditions, such as nipple discharge, breast cysts, or history of breast trauma; radiation exposure; increasing age; and Jewish ancestry have also been associated with an increased risk for breast cancer in men (9). Gynecomastia probably does not represent a significant risk factor. Clinical gynecomastia has been reported in 6% to 38% of cases of breast cancer in men, which suggested that it could be a predisposing factor (15, 16). However, large reviews of gynecomastia in healthy men have found that 35% have clinical gynecomastia (17) and 40% have histologic evidence of gynecomastia (18). Thus, the rates in male patients with breast cancer do not seem to be higher than those in the general population.

GENETICS

Approximately 15% to 20% of male patients with breast cancer have a positive family history, although only 7% of the general male population has an affected family member (15, 19–22). Therefore, researchers have suspected that some families may carry genetic mutations that provide an increased risk for breast cancer. In women, the breast cancer susceptibility genes *BRCA1* and *BRCA2* are thought to account for most hereditary breast cancers. Mutations in these genes confer a 40% to 70% risk for developing breast cancer by age 70 years. In men, *BRCA1* does not appear to be associated with a significantly increased risk for breast cancer, although mutations in this gene have been described in affected men (23). However, men with *BRCA2* mutations are predisposed to breast cancer. This gene was first identified by Wooster, who localized it to 13q12-13 and described multiple cases of breast cancer in men that showed linkage to this area (24). Families in which breast cancer has occurred and at least one male has been affected have been reported to have a 60% to 76% chance of carrying *BRCA2* mutations (25, 26). Thus, the presence of breast cancer in men within a family with documented breast cancer indicates a high likelihood of a *BRCA2* mutation.

The frequency of *BRCA2* mutations in men without a strong family history is much lower. A population-based study from California found that only 2 of 54 cases (4%) had *BRCA2* mutations (21). Other series (Table 2) report that between 11% and 40% of men with breast cancer carry this mutation (27–32). The highest known prevalence of *BRCA2* mutations in male patients with breast cancer is in Iceland, where a founder mutation accounts for 40% of all cases (28). Little is known about the distinguishing characteristics of breast cancer in men with *BRCA2* mutations, although men with a mutation may present with disease at an earlier age (33).

PATHOLOGY

Almost all of the histologic subtypes of breast cancer that have been described in women have also been reported in men. Approximately 90% of all breast tumors in men are invasive carcinomas; the remaining 10% are noninvasive (34). The proportion of noninvasive cancers is higher than that seen in women before the introduction of mammography and may be due to the small size of the male breast, which simplifies the detection of small breast masses (34). Almost all of the noninvasive cancers are ductal carcinoma in situ. Lobular carcinoma in situ is extremely rare because of the absence of terminal lobules in the normal male breast; it has only been reported in conjunction with invasive lobular carcinoma (15, 35, 36). Ductal carcinoma in situ of the male breast differs from that of the female

Table 2. ***BRCA2*** **Mutations in Breast Cancer in Men**

Author, Year (Reference)	Patients Tested	Patients with *BRCA2* Mutations	Patients with *BRCA2* Mutations	Patients with Positive Family History
	n		%	
Couch et al., 1996 (27)	50	7	14	80
Thorlacius et al., 1996 (28)	30	12	40	25
Friedman et al., 1997 (21)	54	2	4	17
Mavraki et al., 1997 (29)	28	3	11	36
Haraldsson et al., 1998 (30)	34	7	21	13
Csokay et al., 1999 (31)	18	6	33	0
Díez et al., 2000 (32)	17	3	18	53

Table 3. **Pathologic Features of Breast Cancer in Men***

Pathologic Feature	Total	Tumors		References
		Positive or Immunoreactive	Positive or Immunoreactive	
	n		%	
Estrogen receptor	1301	1053	81	11, 15, 22, 34, 41–45, 48, 51–82
Progesterone receptor	1040	766	74	15, 22, 34, 43–45, 48, 51–69, 71–73
C-erbB-2†	511	190	37	48, 50, 58–61, 73, 76, 79, 83–88
p53 protein†	472	143	30	48, 57–61, 73, 76, 77, 83, 87, 89–92
bcl-2	193	153	79	60, 61, 83, 93
Cyclin D1	117	60	51	61, 94
EGFR	61	24	39	59, 75

* Data pooled from multiple studies; EGFR = epidermal growth factor receptor.
† Tested by immunohistochemistry.

breast in that almost 75% of cases are a papillary subtype and almost all cases are low to intermediate grade (37).

In men, the predominant histologic subtypes of invasive carcinoma are infiltrating ductal carcinoma, which accounts for more than 80% of all tumors (38–45), and papillary carcinoma, which makes up about 5% (22, 38, 39, 45–47). Lobular carcinoma is much less common in men than in women and represents only 1% of all cases (15, 22, 44). The rarer subtypes, such as medullary, tubular, mucinous, and squamous carcinomas, have all been reported in men, although they may be slightly more uncommon than in women (34, 43–45). Inflammatory carcinoma and Paget disease are seen with similar frequency in men and women (34, 45, 46).

Carcinomas of the male breast have a higher rate of hormone receptor positivity than do carcinomas of the female breast when matched for tumor stage, grade, and patient age (48–50). Our review of the literature indicates that 81% of breast cancers in men are estrogen receptor positive, and 74% are progesterone receptor positive (**Table 3**) (11, 15, 22, 34, 41–45, 48, 51–82). In contrast to women, men do not have a higher incidence of estrogen receptor–positive tumors with advancing age (34, 51, 60, 61).

MOLECULAR MARKERS

C-erbB-2, p53, Bcl-2, cyclin D1, and epidermal growth factor receptor (EGFR) are important in the pathogenesis and prognosis of breast cancer in women. Recent literature has evaluated their role in carcinoma of the male breast, and we present a synthesis of these data (**Table 3**). The *c-erbB-2* protooncogene encodes for a transmembrane receptor of the tyrosine kinase family, which is closely related to EGFR. This protein is expressed in 20% to 30% of breast cancers in women and may be associated with a poor prognosis (95). Pooled data indicate that 37% of tumors overexpress c-erbB-2 as detected by immunohistochemistry (48, 50, 58–61, 73, 76, 79, 83–88). Although these data are the best available, they must be interpreted with caution because antibody preparations and the definitions for positive staining were not standardized and varied considerably among studies. Recently, Bloom and colleagues presented data on 58 male patients who were tested for c-erbB-2 overexpression (88). Twenty-six of these patients had been evaluated in an earlier study, and 35% were reported as overexpressing c-erbB-2 (79). When the same tumors were reevaluated by using stricter criteria to define positive immunohistochemistry staining, only one sample had either 2+ or 3+ staining. This study suggests that the older data may have been overestimating the rate of c-erbB-2 expression. Bloom and colleagues' study also evaluated the patient's tumors by using fluorescent in situ hybridization and found that none of the 58 tumors had gene amplification. This is the only study to date that has used fluorescent in situ hybridization to evaluate *c-erbB-2* gene amplification in breast cancer in men. The results suggest that breast cancer in men may have either low rates of c-erbB-2 expression or protein overexpression without gene amplification. It is unclear whether c-erbB-2 expression is a negative prognostic factor in breast cancer in men. Several small studies have associated c-erbB-2 expression with decreased overall survival (58, 79, 83), but the Mayo Clinic series of 76 men, which is the largest series to date, found no association between c-erbB-2 expression and overall survival (61).

P53 is a tumor suppressor gene that controls cell growth by inducing cell cycle blockade, apoptosis, and cell differentiation. *P53* gene alterations are the most common single genetic abnormality in breast cancer in women and are present in approximately 30% of cases (95, 96). When the *p53* gene is mutated, the abnormal protein accumulates within the cell and can be detected by immunohistochemistry. Several studies have evaluated the incidence of *p53* mutations in breast cancer in men. In our review of the literature, we found 472 cases of breast cancer in men that were tested for *p53* mutations using immunohistochemistry; 143 cases (30%) tested positive for a mutation (48, 57–61, 73, 76, 77, 83, 87, 89–92). These results are similar to data reported for breast cancer in women. The prognostic significance of *p53* mutations in breast cancer in men has not been clearly established, but most studies have found *p53* mutations to be associated with decreased survival (55, 57–60, 87).

Bcl-2 is a protooncogene that inhibits apoptosis and thereby promotes cell growth. In breast cancer in women, expression of Bcl-2 has been associated with favorable prognostic features (97). Several studies have investigated the incidence of Bcl-2 expression in breast cancer in men. Overall, Bcl-2 expression was seen in 153 (79%) of 193 cases (60, 61, 83, 93). Men may have significantly higher rates of Bcl-2 expression than women (60), but Bcl-2 expression has not been shown to have prognostic significance in men (60, 61, 93). The high rates of expression of Bcl-2 in male breast cancer suggest that apoptotic mechanisms may be important in the etiology of breast cancer in men.

Cyclin D1 is involved in cell-cycle regulation and helps control the cell's entry into S phase. In breast cancer in women, this gene is oncogenic but appears to be associated with a favorable prognosis (95). A total of 117 tumors of the male breast were tested for cyclin D1 overexpression; 60 (51%) were immunoreactive (61, 94). This number is very similar to the 50% rate of overexpression seen in women (95). Rayson and colleagues (61) found that cyclin D1 negativity was associated with significantly decreased progression-free survival, indicating that gene overexpression may be a favorable prognostic factor in men with carcinoma of the breast.

The data on EGFR expression are even more limited. Epidermal growth factor receptor is a transmembrane glycoprotein that is present in low levels in normal breast tissue and is overexpressed in 35% to 60% of breast cancers in women (96). Overexpression of EGFR in women is inversely correlated with estrogen receptor expression and may be a negative prognostic factor. Only two studies have reported the rates of EGFR expression in men. Fox and colleagues (75) found that 16 of 21 cases (76%) expressed EGFR, and Willsher and colleagues (59) reported that 8 of 40 cases (20%) showed EGFR expression. No association was found with either estrogen receptor status or with prognosis, although conclusions are limited by very small sample size.

PROGNOSTIC FACTORS AND OUTCOME

As in women, axillary lymph node status, tumor size, histologic grade, and hormone receptor status have been shown to be significant prognostic factors in men with breast cancer. Lymph node involvement is the most important negative prognostic factor for breast carcinoma in men (19, 45, 46, 65, 98). In a series of 335 patients, Guinee and colleagues (98) reported 5-year survival rates of 90% for histologically node-negative disease versus 65% for node-positive disease (98). They also found that the number of involved axillary lymph nodes was predictive of survival, even after adjusting for tumor size, skin involvement, and patient age. The 10-year survival rate for patients with histologically node-negative disease was 84% compared with 44% for one to three positive nodes, and 14% for four or more positive nodes.

Table 4. **Survival Rates for Breast Cancer in Men**

Variable	Survival Rate, %		References
	5-Year	10-Year	
Overall survival	36–66	17–52	11, 15, 19, 44, 45, 47, 100–103
Stage I	55–100	52–89	38, 41, 43, 103, 104
Stage II	41–78	10–52	38, 41, 43, 104
Stage III	16–57	2–23	11, 43, 104
Stage IV	0–14	0	11, 41, 102, 104
Node negative	57–100	43–84	15, 19, 38, 39, 64, 98, 105, 106
Node positive	31–60	11–35	15, 19, 38, 39, 64, 98, 105, 106
Disease-specific survival	52–74	26–51	19, 44, 45, 102, 103

Tumor size has also been shown to be a significant prognostic factor in breast cancer in men (16, 19, 22, 41, 98, 99). In a series of 397 patients in France, 5-year crude survival rates by tumor size were 85% for tumors measuring less than 2 cm in diameter, 63% for tumors 2 to 5 cm, and 51% for tumors greater than 5 cm (19). High histologic grade is similarly associated with decreased survival rates (43, 99, 100). Ribeiro and colleagues (43) found a statistically significant difference in 5-year survival based on histologic grade of tumor (grade 1, 76%; grade II, 66%; and grade III, 43%).

Finally, most evidence points to hormonal status in men being a prognostic factor, although the number and size of studies are limited. A study from Princess Margaret Hospital in Toronto, Ontario, Canada, of 229 patients found that estrogen receptor positivity predicted better overall survival in univariate analysis; but after adjustment for patient age, tumor size, lymph node status, and type of therapy, this difference was no longer significant (15). However, a large study of 215 patients from health care institutions in eastern Wisconsin showed that men with hormone receptor–positive tumors had improved overall survival, even after adjustment for tumor stage and axillary lymph node status (45).

Clinical outcome for men with breast cancer is similar to that for women. Five-year overall survival rates for all stages of breast cancer in men have been reported to range from 36% to 66%, and 10-year overall survival rates range from 17% to 52% (100, 101). Disease-specific survival rates are somewhat higher; 52% to 74% of patients are alive at 5 years and 26% to 51% are alive at 10 years (19, 102). Overall and disease-specific survival rates are shown in **Table 4**. Stage of disease predicts survival rates; overall 5-year survival rates are 55% to 100% for stage I, 41% to 78% for stage II, 16% to 57% for stage III, and 0% to 14% for stage IV disease (11, 38, 39, 41, 43–45, 104).

Although older articles have reported that men with breast cancer have poorer survival rates than women (46, 47), most recent series show that men and women have

Table 5. **Presenting Signs and Symptoms**

Presenting Signs and Symptoms	Frequency, %	References
Breast mass	50–97	15, 16, 19, 43, 44, 103, 104, 107
Nipple retraction	10–51	15, 19, 44, 104
Local pain	4–20	15, 44, 104, 107
Nipple ulceration	4–17	15, 44, 103, 107
Nipple bleeding	2–9	15, 103, 107
Nipple discharge	1–12	15, 16, 19, 44, 103, 104, 107
None	1–2	15, 107

equivalent prognoses when matched for age and stage of disease (19, 48, 60, 101). Men do have lower overall survival rates, but this is probably due to later stage at presentation, more advanced age, and high rates of death from intercurrent illness. The large study done in France of 397 male patients with breast cancer found that 40% of patients died of intercurrent illness (19). Other studies have corroborated this finding (45, 67). The cause of these high death rates in men with breast cancer remains unclear; however, it may in part be due to the older age of these men at presentation.

CLINICAL FEATURES

Approximately 85% of men with breast cancer present with a painless subareolar mass (43). Other common presenting signs and symptoms are nipple retraction, local pain, nipple ulceration, nipple discharge, and nipple bleeding (**Table 5**). Most patients present with more than one sign or symptom (15, 44). The rate of nipple involvement has been reported to be approximately 40% to 50%, perhaps because of the sparsity of breast tissue and the central location of most tumors (58, 105). The disease has a slight predilection for the left breast (16, 44, 45, 107) with a left-to-right ratio of 1.07:1 (5). Bilateral disease is rare. Men are more likely than women to have a delay between the onset of symptoms and a diagnosis of breast cancer, possibly because of the limited public awareness of breast cancer in men. This delay in diagnosis may contribute to men presenting at later stages than do women.

When a man presents with a breast mass, the primary differential diagnosis is gynecomastia versus carcinoma. Mammography can be useful in distinguishing a benign from malignant condition; carcinoma is often eccentric with irregular, spiculated margins (1). Screening mammography has no role in men because of the rarity of the disease and the small size of the male breast, which allows easy palpation of most masses. As in women, a biopsy of any suspicious mass should be performed. Fine-needle aspiration has been evaluated in male patients and has been found to be very sensitive and specific (108). When malignancy is diagnosed, men should have the same staging evaluation as women. The American Joint Committee on Cancer (AJCC) classification is the most widely used staging system and is based on tumor size, presence of nodal metastases, and presence of distant metastases (TNM) (109). Tissue evaluation should include determining tumor grade and hormone receptor status because both have prognostic significance. An algorithm for diagnostic and treatment recommendations is shown in the **Figure**.

LOCAL THERAPY

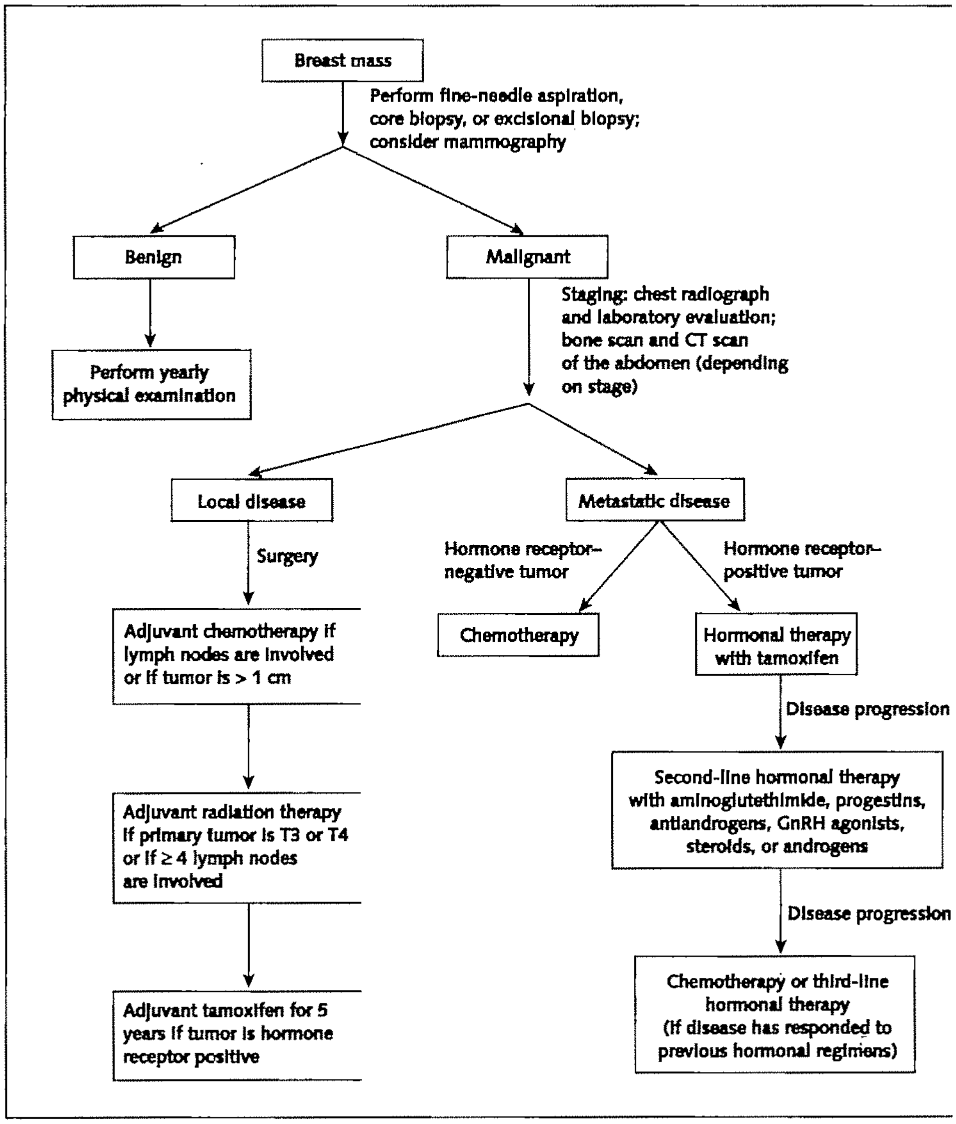
For men who present with nonmetastatic disease, the currently recommended surgical therapy is modified radical mastectomy. Historically, most men were treated with radical mastectomy; however, because women have been shown to do as well with a more limited surgical approach, most men are also now treated with modified radical mastectomies. Studies that have compared radical with modified radical mastectomy in men have found equivalent local recurrence and survival rates for these two surgical approaches (41, 71, 110). Thus, it seems reasonable to recommend less extensive surgery. Because the male breast has sparse amounts of tissue, segmental mastectomy probably does not have a role in the treatment of carcinoma of the male breast. As in women, axillary dissection is an essential part of surgical therapy (16, 19).

Limited data are available for determining which patients need radiation therapy after modified radical mastectomy. Several studies have found that radiation reduces the risk for local recurrence but does not change overall survival (19, 40, 45, 104). Some authors have suggested that the central location of tumors in the male breast may predispose to internal mammary lymph node metastases. They conclude that radiation to the internal mammary nodes should be considered for all patients and that chest wall radiation should be considered for patients with locally advanced disease (111).

ADJUVANT THERAPY

Adjuvant hormonal therapy with tamoxifen in women with estrogen receptor–positive breast carcinoma has resulted in significantly improved survival rates. Because men have high rates of hormone receptor positivity, adjuvant hormonal therapy is theoretically very promising. No randomized clinical trials have evaluated the use of adjuvant tamoxifen. Several large studies have retrospectively compared men who were treated with tamoxifen in an adjuvant setting with men who received no hormonal therapy and have found improved survival in patients treated with tamoxifen (15, 43, 63). Ribeiro and Swindell (63) compared 39 patients with stage II and stage III disease who received tamoxifen with historical controls and found a 5-year survival of 61% versus 44%, suggesting a significant benefit from tamoxifen (63). The studies of adjuvant tamoxifen may underestimate its benefit because most men were treated for less than 2 years. The optimal length of therapy in women is 5 years; therefore, a greater benefit in men may been seen with longer duration of therapy. Based on the available data, we recommend that all men with hor-

Figure. Treatment recommendations for breast cancer in men.


Breast mass
Perform fine-needle aspiration, core biopsy, or excisional biopsy; consider mammography
Benign
Malignant
Perform yearly physical examination
Staging: chest radiograph and laboratory evaluation; bone scan and CT scan of the abdomen (depending on stage)
Local disease
Metastatic disease
Surgery
Hormone receptor–negative tumor
Hormone receptor–positive tumor
Adjuvant chemotherapy if lymph nodes are involved or if tumor is > 1 cm
Chemotherapy
Hormonal therapy with tamoxifen
Disease progression
Adjuvant radiation therapy if primary tumor is T3 or T4 or if ≥ 4 lymph nodes are involved
Second-line hormonal therapy with aminoglutethimide, progestins, antiandrogens, GnRH agonists, steroids, or androgens
Disease progression
Adjuvant tamoxifen for 5 years if tumor is hormone receptor positive
Chemotherapy or third-line hormonal therapy (if disease has responded to previous hormonal regimens)

CT = computed tomography; GnRH = gonadotropin-releasing hormone.

mone receptor–positive tumors be treated with tamoxifen for 5 years.

The role for adjuvant chemotherapy in men is less established, but the limited data do suggest a benefit. Given the considerable toxicity of chemotherapy, few men with early-stage disease have received chemotherapy; thus, even retrospective data have been difficult to obtain. The National Cancer Institute studied 24 male patients who were given adjuvant chemotherapy for node-positive stage II breast cancer (69). The 5-year survival rate among treated patients was 80%, which was significantly better than the survival rates among historical controls. The experience with adjuvant anthracycline therapy was reviewed at M.D. Anderson Cancer Center (70). Eleven node-positive patients who were treated with adjuvant chemotherapy (10 with an anthracycline-based regimen) were found to have an estimated 5-year survival rate of greater than 85%, which was substantially better than survival rates of historical controls. Other authors have also found improved outcomes in patients treated with adjuvant chemotherapy (16, 42, 45). With most data supporting a benefit of adjuvant chemotherapy in men and the clear benefit for adjuvant chemotherapy in women, we would offer adjuvant chemotherapy to men who have substantial risk for recurrence. Because there are no data with which to determine exactly which men will benefit from adjuvant chemotherapy, we use the same guidelines in men as in women and offer chemotherapy to men with node-positive disease or primary tumors that are larger than 1 cm.

THERAPY FOR METASTATIC DISEASE

Hormonal therapy has been the mainstay of treatment for metastatic carcinoma of the male breast for the past 5 decades. Initial hormonal therapies were ablative orchiectomy, adrenalectomy, and hypophysectomy. Farrow and Adair (112) described the first response to orchiectomy in 1942, and orchiectomy became the standard of care for treatment of metastatic disease. Jaiyesimi and colleagues reviewed ablative therapies in 447 patients and found response rates of 55% for orchiectomy, 80% for adrenalectomy, and 56% for hypophysectomy (1). Patients who responded to orchiectomy were more likely to respond to second-line ablative therapies, and responding patients had improved survival (113).

Additive hormonal therapy has also been shown to have substantial response rates in metastatic breast carcinoma in men. It is an appealing alternative to ablative therapies because such therapy is reversible, avoids surgical morbidity and mortality, and is psychologically more acceptable to most men than orchiectomy. Overall rates of response to the various additive therapies have been reported as 75% for androgens, 57% for antiandrogens, 50% for steroids, 32% for estrogens, 50% for progestins, 40% for aminoglutethimide, and 49% for tamoxifen (1). These numbers may be optimistic because responders are more likely to have been reported in the literature. Estrogen receptor positivity appears to predict response to hormonal therapy. Jaiyesimi and colleagues found that 69% of 35 men with estrogen receptor–positive tumors responded to hormonal manipulation compared with 0% of 8 men with estrogen receptor–negative tumors (1). We recommend tamoxifen as first-line hormonal therapy because of its established efficacy in men and limited toxicity. In addition, most oncologists have considerable experience with this drug in women.

Systemic chemotherapy, which is another option for men with metastatic breast cancer, is usually reserved for second-line therapy because most men will respond to hormonal manipulation. One study directly compared chemotherapy with hormonal therapy and found superior response rates in patients treated with hormonal therapy (114). Chemotherapy, however, can offer significant palliation to men in whom hormonal therapy has failed or those with hormone receptor–negative disease. Response rates reported in the literature are 67% for 5-fluorouracil, doxorubicin, and cyclophosphamide; 55% for doxorubicin and vincristine; 53% for cyclophosphamide; 33% for cyclophosphamide, methotrexate, and 5-fluorouracil; and 13% for 5-fluorouracil (1). For all other regimens or single agents, fewer than five cases have been reported in the literature. For all chemotherapy regimens, the overall response rate was 40% (1).

CONCLUSIONS

Carcinoma of the male breast has many similarities to breast cancer in women, but the diseases have different genetic and pathologic features. Both *BRCA1* and *BRCA2* mutations can cause breast cancer in women, but only *BRCA2* mutations confer a significant risk to men. Noninvasive carcinomas in men are all low- to intermediate-grade ductal carcinoma in situ; pure lobular carcinoma in situ is extremely rare. Most invasive carcinomas are infiltrating ductal, with lobular carcinoma representing only about 1% of invasive disease. Men have higher rates of estrogen and progesterone positivity than do women but similar percentages of c-erbB-2, p53, cyclin D1, and EGFR overexpression. Men may be more likely to have tumors that overexpress bcl-2, but the clinical significance of this finding is not clear.

The diagnostic evaluation and staging of breast cancer in men is similar to that in women. For localized disease, modified radical mastectomy is the preferred surgical approach. There is no evidence that adjuvant radiation therapy after mastectomy improves survival, although men may have a higher risk for internal mammary lymph node metastases and in theory could benefit from internal mammary radiation therapy. Although the evidence is limited, most studies point to a benefit from both adjuvant tamoxifen and chemotherapy. Given the known benefit of adjuvant therapy in women, we recommend that men also be offered adjuvant therapy using the same guidelines that are the standard of care for women. Metastatic disease can be treated with either hormonal therapy or chemotherapy. Because men have high rates of response to additive hormonal therapy, this approach is recommended for first-line treatment in hormone receptor–positive disease. Tamoxifen is the most accepted front-line additive therapy. Selective aromatase inhibitors (anastrozole and letrozole) have been approved for first-line treatment of metastatic breast cancer in women, but there are no published reports of responses in men. Chemotherapy can be of use for hormone-refractory disease.

Areas for future investigation are plentiful. Larger studies of pathologic markers would be helpful to define which genetic abnormalities play a role in breast cancer in men and to determine which markers are important prognostic factors. The role of adjuvant hormonal and chemotherapy deserves further study, especially to determine which subgroups of men will benefit. New hormonal and chemotherapeutic agents, such as selective aromatase inhibitors and taxanes, deserve investigation for the therapy of carcinoma of the male breast. Finally, men should be strongly encouraged to participate in clinical trials so that prospectively gathered information will be available and more can be learned about breast cancer in men.

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New Federal Initiatives To Enhance the Medical Treatment of Opioid Dependence

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Opioid dependence is a chronic relapsing medical condition with substantial health and societal complications. Recent federal initiatives are designed to enhance the medical treatment of patients with opioid dependence and will expand the role of internists in the care of these patients. These initiatives include a process for federal exemptions to allow for pharmacologic treatment in office settings, waivers for the use of new medications, and new rules governing the oversight and distribution of opioid agonist medications for maintenance treatment. This perspective describes these initiatives and their implications for internists.

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Opioid dependence is a chronic medical disorder that is manifested by the repeated self-administration of opioids (1–6). Research has demonstrated the neurobiological changes in cellular and molecular systems that result from repeated exposure to short-acting opioids. These changes include perturbations in opioid receptor kinetics, transmembrane signaling, postreceptor signal transduction, and intracellular messengers (5, 6). The physiologic dependence and addictive behavior that are diagnostic of opioid dependence result from these neurobiological changes and form the rationale for prescribing opioid agonist medications for the treatment of opioid dependence (3). These medications stabilize brain neurochemistry by replacing short-acting euphorigenic opioids (for example, heroin) with long-acting noneuphorigenic opioids (for example, methadone). They have two main mechanisms of action: 1) cross-tolerance at the opioid receptor, which prevents opioid withdrawal, and 2) competition for opioid receptor binding sites, which blocks the effects of exogenously administered opioids (3, 7).

HISTORICAL ROLE OF THE FEDERAL GOVERNMENT IN THE TREATMENT OF OPIOID DEPENDENCE

During the 20th century, the U.S. federal government played a considerable role in regulating the medical treatment of opioid-dependent patients (8). The Harrison Narcotic Act, adopted by Congress in 1914, resulted from a series of legislative efforts designed to control the medical practice of using opioid medication, such as morphine, for the treatment of opioid-dependent patients. This early legislation set the stage for future federal control over this aspect of practice (9). Successful treatment of opioid dependence with methadone by Dole and colleagues in the 1960s (7, 10) was followed by a series of federal regulations and legislation, such as the Narcotic Addict Treatment Act (NATA) of 1974, with a twofold agenda: to ensure the quality of maintenance treatment with methadone and to prevent diversion of methadone for illicit use (4). The NATA created joint responsibility for methadone between the U.S. Food and Drug Administration (FDA), which had responsibility for the public health and safety, and the U.S. Drug Enforcement Administration (DEA), a branch of the Department of Justice, which had responsibility for law enforcement and diversion control (8).

These federal regulations, which are unique for an approved and effective medical therapy (1, 11, 12), have engendered criticism that they do not reflect clinical research on the effectiveness of methadone or the current understanding of opioid dependence (8, 13). Designed almost 30 years ago when there was a different understanding of opioid dependence and the role of opioid agonist treatment, the regulations and laws were originally developed to limit inappropriate prescribing practices and methadone diversion. Recent reviews of the narcotic treatment system by federal agencies (for example, by the General Accounting Office) and independent bodies (for example, the Institute of Medicine), however, have determined that the system by which the FDA regulates and monitors the use of opioid medications is too heavily oriented toward administrative requirements and focuses too little on treatment outcomes (13). These reviews cite the large variability in treatment outcomes with methadone (13, 14) and fault a regulatory system that promotes process-oriented evaluations that lack clinical orientation over medical judgment and patient outcomes.

At the end of the 20th century, federal regulations for methadone maintenance treatment, which were codified in the *Federal Register,* delineated medical practice for methadone: which patients could receive treatment, the appropriate amount of counseling support, medication dosing limits, frequency of monitoring for illicit drug use, physician and staff qualifications and ratios, and criteria for determining which patients were candidates for unsupervised use of medication (8). In addition, these regulations specified special licensure for physicians prescribing methadone for maintenance treatment and mandated a separate registration from the DEA.

These regulations have resulted in a system that is restricted primarily to large urban narcotic treatment programs that primarily provide care for opioid-dependent patients, some of whom continue to use illicit drugs (14). In this system, receiving medication for opioid dependence meant visits to a clinic 6 of 7 days per week for medication dispensing, often for as long as 2 years, which created significant logistical constraints (15). Unobserved dosing of medication was generally contingent on evidence of abstinence through urine toxicology analysis. This treatment system, rather than promoting treatment entry and retention, was perhaps partly responsible for the fact that only 170 000 of the estimated 810 000 opioid-dependent patients in the United States were receiving medication for this medical condition (16). We describe the new federal initiatives that have been implemented over the past 2 years, which are designed in part as a response to the deficiencies of this situation.

NEW FEDERAL INITIATIVES

New federal initiatives for the care of opioid-dependent patients come at a time of increasing heroin use and high rates of HIV and hepatitis C virus transmission among injection drug users (17). Although funding for traditional narcotic treatment programs could be raised in an effort to expand treatment capacity, this solution would not necessarily increase involvement of the medical profession in the care of opioid-dependent patients or serve the subset of patients who choose not to enter narcotic treatment programs. The current initiatives are designed to meet the dual objectives of treatment expansion and the involvement of physicians in the care of opioid-dependent patients. The changes are designed to create a new and more clinically oriented treatment system for the 21st century that reflects the recognition that opioid dependence is a medical disorder and that methadone and other pharmacotherapeutic agents are currently the most effective treatments for this disorder (13).

The unifying theme among these unique initiatives is the movement toward a system that resembles care provided for other chronic medical conditions and that allows more clinician involvement. These important federal legislative and regulatory efforts reflect a desire to rethink the clinical and public health implications of federal policy to help achieve several critical goals. These goals include 1) increasing the participation of the medical community in the treatment of opioid-dependent patients, 2) increasing the focus on patient needs, 3) improving treatment outcomes, 4) reducing variability in the quality of services, 5) making federal oversight more effective, and 6) expanding access to treatment (13). In the following sections, we discuss three recent landmark changes to federal regulation that will facilitate office-based medical maintenance and the use of independent physicians' offices to coordinate opioid agonist therapy and the medical care of opioid-dependent patients (Table 1).

Exemptions for Office-Based Opioid Agonist Treatment

A federal advisory, released jointly on 30 March 2000 by the FDA and the Center for Substance Abuse Treatment (CSAT), voiced support for narcotic treatment program-based exemptions to allow for office-based methadone maintenance (18). Under the exemption process, a narcotic treatment program may apply to the CSAT for an exemption from any regulatory requirement. This would allow, for instance, an exemption to be granted to establish office-based methadone maintenance. These requests for exemptions will be reviewed and action taken after consultation with the DEA and the state methadone authority.

Table 1. **Federal Initiatives To Enhance the Medical Treatment of Opioid Dependence**

New Initiative	Type of Initiative	Status
Exemptions for office-based opioid agonist treatment	Advisory: Center for Substance Abuse Treatment and U.S. Food and Drug Administration	Active
Prescribing new medications for office-based maintenance and detoxification	Legislation: Drug Addiction Treatment Act of 2000	Active*
New regulations to reflect the effectiveness of opioid agonist medications	Rule: Published in the *Federal Register*	Active

* No schedule III, IV, or V medications are approved for the indication of maintenance or detoxification treatment of opioid dependence. Buprenorphine and the buprenorphine–naloxone combination are currently under consideration for this indication by the U.S. Food and Drug Administration.

Successful office-based demonstrations using research mechanisms (19–22) and ongoing programs in New York, Baltimore, and Seattle have provided information about the appropriate conduct of these types of programs and have contributed to the CSAT's process of developing clinical practice guidelines and training curricula for office-based practitioners (18). This advisory represents an evolution of these programs from research into clinical practice. New rules governing opioid agonist medication provide for longer periods of unobserved medication dispensing and favor a system with linkages between narcotic treatment programs and physicians' offices. The text accompanying the new rules supports the development of additional information and experience with office-based care to evaluate and refine these treatment models (23).

Prescribing New Medications for Office-Based Maintenance and Detoxification

On 17 October 2000, PL 106-310, the Drug Addiction Treatment Act of 2000, was signed into law (Table 2). This legislation allows qualifying physicians to prescribe schedule III, IV, and V narcotic medication or combinations of such medications for treating opioid dependence (24). The Act stipulates that physicians must use medications that have been approved by the FDA for maintenance and detoxification treatment of opioid dependence and must notify the Secretary of the Department of Health and Human Services (DHHS) of their intention to provide this treatment. The first medications anticipated to be approved by the FDA for this indication are the partial opi-

Table 2. **Summary of Federal Legislation Included in the Drug Addiction Treatment Act of 2000**

Medication
Permits the use of approved narcotic medications in schedule III, IV, or V for maintenance or detoxification treatment by qualifying physicians
Qualifying physician
Licensed under state law and meets one of the following criteria
Certified by a subspecialty board in addiction psychiatry by the American Board of Medical Specialties
Certified in addiction medicine by the American Society of Addiction Medicine or the American Osteopathic Association
Completed a minimum of 8 hours of approved training in the treatment and management of opiate-dependent patients
Served as an investigator in a clinical trial leading to drug approval
Has training or experience deemed appropriate by the state medical licensing board or the Secretary of the Department of Health and Human Services
Practice criteria
Physician is able to refer patients to counseling and ancillary services
Limit of 30 patients per physician or group practice

oid agonist buprenorphine and the buprenorphine–naloxone combination (25).

The Drug Addiction Treatment Act defines qualified physicians as those with state licenses and certification in addiction medicine through subspecialty boards or medical societies. In addition, physicians may become qualified by participating in a minimum of 8 hours of approved training (through the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, or the American Psychiatric Association) in the treatment and management of opioid-dependent patients. Finally, physicians may be considered qualified at the determination of a state medical licensing board or the Secretary of the DHHS. The law stipulates that providers are limited to 30 concurrent patients receiving this type of treatment in their practice and must be able to refer patients to appropriate counseling and ancillary services. To assist physicians, the Act stipulates that a treatment improvement protocol containing science-based, best-practice guidelines for the treatment and maintenance of opioid-dependent patients will be produced.

New Regulations To Reflect the Effectiveness of Opioid Agonist Medications

New rules published in the *Federal Register* on 17 January 2001 that took effect on 17 May 2001 transferred administrative responsibility for the use of narcotic drugs in maintenance and detoxification treatment from the FDA to the Substance Abuse and Mental Health Service Administration, the DHHS agency in charge of administering federal programs related to substance abuse treatment, service, and prevention (**Table 3**) (23). The rule replaces the FDA's inspection-oriented oversight with an accreditation-based system that is designed to focus more on clinical outcomes. In addition, significant changes in the rules that allow for dispensing of solid methadone (previously, only liquid methadone was allowed) and the unsupervised use of solid or liquid methadone for up to 4 weeks are designed to increase flexibility, patient adherence, and retention in treatment. Finally, in an effort to foster physician involvement in the treatment of opioid-dependent patients, the rule supports the development of linkages between narcotic treatment programs and office-based physicians for the treatment of stabilized patients by using an exemption process (described earlier) designed to replace the previous research-based system.

IMPLICATIONS OF THE NEW FEDERAL REGULATIONS FOR PRACTICE, RESEARCH, AND EDUCATION

Clinical, research, and education initiatives are needed to accompany these new legislative efforts to help ensure that opioid-dependent patients receive the highest quality of care. To date, treatment of substance use disorders in general and opioid dependence in particular has unfortunately occurred outside of standard medical practice. This situation exists despite the relatively high prevalence of these disorders (26–28) and the recognition that these disorders are chronic medical conditions (4). Long-standing federal regulations that have controlled the use of methadone and other pharmacotherapeutic agents for the treatment of opioid dependence have undoubtedly contributed to this situation by moving many of the components of diagnosis, assessment, and treatment to specialized narcotic

Table 3. **Summary of Changes in Federal Regulations for the Use of Narcotic Drugs in Maintenance and Detoxification Treatment of Opioid Addiction**

Regulation	Previous	Revised
Administrative responsibility	U.S. Food and Drug Administration	Substance Abuse and Mental Health Services Administration
Program approval	Process oriented	Accreditation based
Methadone formulations allowed	Liquid only	Liquid and solid
Maximum schedule for medications dispensed for unsupervised use	6 days after 3 years of supervised dispensing	6 days after 270 days, 2 weeks after 1 year, and 1 month after 2 years of supervised dispensing
Justification for doses >100 mg	Required	Not necessary
Office-based treatment	Special arrangements (e.g., investigational new drug)	Program authorizations and exemptions

treatment programs and outside of the realm of most physicians. These new rules and regulations are designed to increase clinical judgment and quality of services and outcomes and to expand access. They will appropriately increase physician involvement and move toward a system that resembles care for other chronic medical conditions and that creates opportunities for new clinical practice, research, and education.

For the first time, qualified physicians, as outlined in the new legislation, will be able to provide effective medication for treating both stabilized patients and new patients seeking treatment. This will help expand access to patients who previously resisted seeking treatment because of concerns about confidentiality or stigma. It is likely that the first physicians providing this care will be those with previous experience and certification in addiction medicine. As experience develops, however, physicians in locations with a high prevalence of opioid dependence and those in remote areas without specialized treatment programs will be among those who are likely to adopt this type of medical practice. Individual practitioners will have to tailor the delivery of services to their local environments. For example, a rural practitioner might need to provide a greater range of on-site services (for example, counseling or urine toxicology testing) than a physician practicing in an area with many nearby services.

Effective implementation of these new initiatives faces myriad potential barriers. These include physician acceptance, patient acceptance, the need for reimbursement mechanisms that allow physicians to provide services that might otherwise be handled through referral to a mental health or substance abuse service, logistic considerations for the physician's office (for example, urine toxicology testing), inappropriate prescribing by physicians, medication diversion, and appropriate strategies for patient confidentiality.

To aid physicians and patients in this transition, special efforts are needed to help guarantee that essential components of a system of care are in place and that the requisite services are available. Physician training programs and resources have been designed to address specific areas in the care of opioid-dependent patients; they include office logistics, appropriate prescribing behavior, risk for medication diversion, and steps to maintain patient confidentiality (29–32). The CSAT has convened a consensus panel to develop a guide for implementing office-based programs that can be used by physicians and narcotic treatment programs. Finally, the Drug Addiction Treatment Act of 2000 requires that the Secretary of the DHHS issue a practice guideline. Additional research will be needed to evaluate the effectiveness of these programs and to help determine the appropriate role of psychosocial services in office-based practice.

International experience can provide helpful information for future efforts in the United States. Several countries, including the United Kingdom, Australia, and France, have adopted regulations that allow physicians to prescribe opioid agonist maintenance treatment. In Scotland, specialized support service programs for general practitioners have been developed to assist in physician and patient acceptance (33). In Britain, a recent study evaluating the impact of treatment setting (general practice vs. specialist drug clinic) found no difference in treatment outcomes (34). In France, general practitioner satisfaction with the provision of office-based buprenorphine was highest in those practitioners who had cared for injection drug users within the previous year and in those who felt at ease when providing care for these patients (35).

Priorities for research on physician-delivered, office-based care include the identification of appropriate patients, the appropriate level of psychosocial counseling, the determinants of patient and provider satisfaction, the identification of cogent clinical outcomes, the development of appropriate quality of care measures, and evaluation of the cost-effectiveness of this new model of care. Education efforts are needed throughout the medical education system to increase physician understanding of the neurobiological basis of opioid dependence (5, 6, 36), the pharmacology and effectiveness of opioid agonist maintenance, the impact of medical and psychiatric comorbidity, and the role of counseling in treating this disorder.

Current legislative restrictions on the training of physicians who are allowed to provide medication for maintenance and detoxification of opioid-dependent patients can be viewed as a necessary requirement that will improve the likelihood of favorable outcomes for patients. Nonetheless, clinical competence is difficult to mandate, and the medical education system will have to support mechanisms that develop appropriate practice patterns by physicians and allow for increased training and experience in caring for opioid-dependent patients. With appropriate training, clinical experience, guidance, and effective pharmacotherapies, office-based physicians have shown that they can treat complex and stigmatized disorders, such as depression (37, 38) and HIV infection (39). Physicians who are interested in providing care for opioid-dependent patients can turn to specialized training programs being offered nationally by specialty societies, such as the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry. The current changes in federal regulations indicate that it is time for physicians to increase their involvement in the care of patients with opioid dependence in an effort to improve the quality of care for these patients.

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EDITORIAL

Rare Outcomes, Common Treatments: Analytic Strategies Using Propensity Scores

When treated patients are compared to controls, differing outcomes may reflect either effects caused by the treatment or differences in prognosis before treatment. Random assignment of patients to treatment or control, as in a randomized, controlled clinical trial (1), ensures that the groups were comparable before treatment and the prognosis in treated and control groups was nearly the same, so that differing outcomes indicate treatment effects. Somewhat more precisely, random assignment ensures that the only differences in prognosis between groups are due to chance, the flip of a coin in assigning treatments. In an ideal randomized trial, if a common statistical test rejects the hypothesis that the difference in outcomes is due to chance, a treatment effect is demonstrated. Notice that randomization does nothing to make patients have individually similar prognoses; rather, it ensures that assignment to treatment or control is unrelated to prognosis.

When random assignment is not used—that is, in an observational study—treated and control groups may differ in prognosis, and differing outcomes may not be effects of the treatment. Measured and recorded differences in prognosis—overt biases—can often be controlled by analytical adjustments (2), whereas unmeasured differences—hidden biases—may exist and must be addressed by other means (2–4). A prognostic variable or covariate is a variable describing the condition of patients before treatment. *Bias* refers to systematic differences between treated and control groups with respect to one or more prognostic variables; the bias is overt if the variable is measured and hidden if it is not.

Analytical adjustments for overt biases are of two kinds: 1) those that focus on the relationship between prognostic variables and outcomes and 2) those that focus on the relationship between prognostic variables and assignment of patients to treatment or control. The first strategy models the response directly, for example, through use of regression or logistic regression. The second strategy, which uses propensity scores, is an attempt to reconstruct, after the fact, a situation similar to random assignment, albeit only with respect to observed prognostic variables. In principle, either strategy (separately or in combination), properly used, can control overt biases. Neither strategy does much to control hidden biases. In practice, the second strategy has advantages over the first when the outcome is rare, the treatment is common, and there are many prognostic variables. Here, the terms *rare* and *common* refer to the available data: A rare outcome is seen in a small fraction of the patients under study, and thus there are limited data with which to model the outcome and its relationship to prognostic variables; however, a large fraction of patients received each of the two treatments under study, so there are plenty of data with which to model the relationship between treatment assignment and prognostic variables. An example of this can be seen in studies of relatively rare adverse side effects of relatively common treatments. One such study is by Jasmer and colleagues (5) in this issue: The authors examined 18 cases of hepatotoxicity among 411 patients given one of two competing treatments for latent tuberculosis infection.

PROPENSITY SCORES: WHAT THEY ARE, WHY THEY WORK, WHAT THEY CAN'T DO

The *propensity score* is the chance of receiving the treatment rather than the control for a patient with given observed prognostic variables (6–8). In the simplest randomized experiment, a coin is flipped to assign patients to treatment or control, so the propensity score is 1/2 for every patient. In contrast, in an observational study, without random assignment, the chance of being assigned to one treatment or another may vary from patient to patient depending on prognostic variables (for example, frail patients may be less likely to be treated surgically, or, as in Jasmer and colleagues' study, patients with other risk factors for liver injury may be less likely to receive a particular tuberculosis treatment). In that case, certain types of patients will be overrepresented in the treated group, and other types will be overrepresented in the control group; as a result, the groups will not be comparable.

An adjustment using propensity scores attempts to undo the problem created by unequal chances of receiving treatment. It does this by comparing patients who had the same chance of receiving treatment. A treated patient who had a 3/4 chance of receiving treatment is compared to a control who also had a 3/4 chance of receiving treatment, while a treated patient who had a 1/4 chance of receiving treatment is compared to a control who also had a 1/4 chance of receiving treatment. If two patients both have a 3/4 chance of receiving treatment on the basis of their observed prognostic variables, these variables will not help to predict which one receives treatment; thus, the comparison is expected to be balanced with respect to these prognostic variables (2, 6). For instance, in a report by Rosenbaum and Rubin (6), patients with good left ventricular function and substantial occlusion of several coronary arteries were more likely to be treated with coronary artery bypass graft surgery, while patients with poor left ventricular function or fewer occlusions of the arteries were more likely to be treated with drugs; as a result, the surgical and drug groups were different in terms of prognostic variables. Indeed, they differed significantly on 74 observed prognostic variables. To control for this, the authors grouped patients into five strata of the same size by using their estimated chance of receiving surgery based on the 74 prognostic variables: that is, using the quintiles of their estimated propensity scores. Within these five strata, all 74 prognostic variables were balanced. Within each of the five strata, the patients in the surgery and drug groups had similar distributions of the 74 prognostic variables. In fact, the balance on observed variables was slightly better than would be expected from random assignment of treatments. Of course, propensity scores balance just observed covariates used to construct the score, but randomization balances both observed and unobserved covariates. Propensity scores can remove overt biases, but unlike randomization, they cannot be expected to remove hidden biases.

RARE OUTCOMES, COMMON TREATMENTS

If the outcome is rare but the treatment is common, there may be little data with which to estimate the relationship between outcome and prognostic variables but plenty of data with which to estimate the relationship between treatment assignment and prognostic variables, that is, to estimate the propensity score. In this case, adjustments using the propensity score may be practical, whereas adjustments based on modeling the outcome may not. Logistic regression is a method used to model a binary (two-category) outcome. If several hundred patients are assigned to each of two treatments and 20 binary outcome events occur, then a logistic regression model for the propensity score may incorporate 30 prognostic variables, but a logistic regression model for the outcome cannot. This situation is not uncommon in studies of relatively rare side effects of standard drugs. (Standard logistic regression is not even possible unless the number of events is greater than the number of prognostic variables—otherwise, the maximum likelihood estimate does not exist—and many more events are needed for a stable model. If a small category of patients in a study, say 10 patients who incidentally have asthma, contains no side effects, then logistic regression will say that patients with asthma will never have side effects, even though there are very few data to warrant such a claim.)

In their study of treatments for latent tuberculosis infection, Jasmer and colleagues compare hepatotoxicity after treatment with isoniazid or rifampin plus pyrazinamide. Of the 411 patients for whom liver enzyme tests at 1 or 3 months were available (about half of whom received isoniazid), only 18 cases of grade 3 or 4 hepatotoxicity occurred; as result, there is little hope of building a good model relating grade 3 or 4 hepatotoxicity to prognostic variables. Patients were allocated to isoniazid or rifampin plus pyrazinamide in alternate weeks. Thus, although the study is not randomized, large biases would not be anticipated under normal circumstances.

Jasmer and colleagues estimated the propensity score—the probability of receiving isoniazid given observed prognostic variables—using a logistic regression model, and then stratified patients into five groups using the quintiles of the estimated score (6). Within these five strata, they found more cases of grade 3 or 4 hepatotoxicity in patients receiving rifampin plus pyrazinamide than in those receiving isoniazid.

Propensity scores can be used in several other ways. One application forms matched pairs of a treated patient and a control with similar propensity scores (7, 9). Another uses a logistic regression model to predict the treatment, in this case isoniazid or rifampin plus pyrazinamide, from prognostic variables plus the outcome, in this case hepatotoxicity; the model rejects the hypothesis that treatment has no effect on the outcome if the coefficient of outcome is a statistically significant predictor of treatment (2, 10). Provided that the treatment is common, this technique is practical even if the outcome is rare. All three approaches can be used in conjunction with models for the outcome; for an example, see Rosenbaum and Rubin's paper (6). When the comparison is not between treatment and control but rather between several doses of treatment, propensity score methods may still be used if the doses can be predicted from the prognostic variables by an ordinal logistic regression model (8, 11). A user of propensity scores should be aware of certain technical issues that are summarized briefly with limited technical detail in encyclopedia entries (10, 12, 13), and in greater technical detail in a textbook (2).

ADDRESSING HIDDEN BIASES

Propensity scores remove overt biases but do little or nothing to address hidden biases due to unobserved or unrecorded differences between treated and control patients before treatment. In an ideal clinical trial, randomization prevents hidden biases, although even experiments may need to address some hidden biases from protocol violations, such as frequent withdrawals of patients from treatment or extensive nonadherence by patients. In contrast, in an observational study, hidden bias is a serious and central problem that could undermine the study's conclusions.

The problem of hidden bias cannot be eliminated from an observational study, although it can often be reduced in magnitude, and it can always be discussed with candor (2, 13). A sensitivity analysis indicates the magnitude of hidden bias that would need to be present to materially alter the conclusions of a study (2–4, 13). For instance, although hidden bias could, in principle, explain away the association between heavy smoking and lung cancer, the magnitude of such a hidden bias would have to be enormous; thus, that association is highly insensitive to hidden bias (3). In contrast, the association between coffee consumption and myocardial infarction (14), although potentially a serious public health concern, is sensitive to comparatively small hidden biases (2). A finding that is sensitive to small hidden biases needs to be viewed with greater caution; however, a sensitivity analysis does not demonstrate that the postulated hidden bias is present. As a result, a conclusion that is sensitive to small biases may nonetheless be correct and should not be dismissed on that basis. A sensitivity analysis is simply a device for candidly discussing and measuring the possible impact of hidden bias, which varies markedly from one study to the next. For a recent example, see Normand and colleagues' analysis (15). Familiar devices intended to shed light on hidden biases, such as Sir Austin Bradford Hill's famous criteria for causality (16) (for example, coherence, specificity, and a dose–response relationship), may be appraised in terms of their ability to reduce sensitivity to hidden bias (2, 13, 17).

SUMMARY

If many patients receive each of two competing treatments but the outcome under study rarely occurs, then there may not be enough data with which to model the relationship between the outcome and prognostic variables. However, there may be plenty of data with which to model the relationship between treatment assignment and prognostic variables. In this situation, among the several methods of adjustment for overt biases, the propensity score method has the advantage of not requiring modeling of the rare outcome event. The propensity score allows us to address the difficult problem of whether a rare outcome event is attributable to a treatment by simultaneously controlling for many measured covariates, even when there are too many covariates to model their relationships with the rare outcome. The principal limitation of all methods of adjusting for overt biases is that they do not address hidden biases from prognostic variables that were not measured. Hidden biases must be addressed by other means.

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Hair It Is: The Long and Short of Monitoring Antiretroviral Treatment

Potent combination antiretroviral therapies have favorably altered the natural history of HIV infection in the United States. Suboptimal drug concentrations are major predictors of treatment failure and the emergence of viral mutations that confer resistance. Nonadherence seems the most common reason for suboptimal drug levels (1). The ability of patients to adhere to antiretroviral regimens may be influenced by regimen complexity, recreational drug use, depression, lack of education, cost considerations, unstable living situations, side effects, and personal beliefs about the safety and efficacy of the drugs (1, 2). Drug level may also be influenced by coadministration of medications and nontraditional treatments that induce the metabolism or efflux pumping of antiretroviral drugs (3). In addition, the bioavailability of some antiretroviral agents is marginal and can be further reduced by gastrointestinal conditions, which are common in patients with AIDS.

Many methods have been evaluated for determining adherence to antiretroviral therapies, including self-report, pill counting, tracking cap-opening events, and measuring drug concentrations in blood and urine (4). These techniques tend to assess behavior over short periods (even self-report, which can be provided for long periods, is considered accurate for only the short term). Use of medication organizer containers and different sources of medication can interfere with pill-counting and cap-opening adherence measures. Measurement of drug levels in plasma is the most sensitive indicator of treatment adequacy; however, plasma levels reflect only the medication doses administered within 1 to 2 days of sampling, and they have limited predictive value for long-term treatment outcomes (5). The ideal measure of medication exposure would be objective, would assess drug levels over relatively long periods, and would not be influenced by medication source and formulation.

Methods that use hair to measure drug levels have primarily appeared in the forensics literature for assessing exposure to drugs of abuse. The potential of hair analysis for therapeutic monitoring, however, is becoming generally recognized. Because the level of drugs in hair reflects uptake from the systemic circulation over an extended time window (weeks to months), hair analysis provides an advantage over blood or urine testing in assessing long-term adherence. In this issue, Bernard and colleagues assessed the concentration of indinavir (a commonly used HIV protease inhibitor) in hair among patients with HIV infection and its relationship to key indicators of outcome, including the amount of viral RNA present in plasma (viral load) and the occurrence of antiretrovirus-resistant mutations (6). This article confirms earlier observations (7, 8) that indinavir levels in hair are significantly higher among patients achieving undetectable plasma HIV RNA levels than in patients with incomplete virologic suppression.

Because antiretroviral resistance in HIV therapy is mediated by selective pressure in the presence of a drug, treatment failure with wild-type (no resistance mutations) virus has been commonly observed and is associated with low medication concentrations in blood. Bernard and colleagues found similar associations with hair levels of indinavir: Patients with the lowest drug levels in hair often failed to respond well to indinavir therapy with wild-type (not drug-resistant) viral strains, and patients with mid-range drug levels in hair often failed to respond to indinavir therapy with drug-resistant viral strains. In this study, patients with the highest levels of indinavir in hair tended to have undetectable viral load levels and the most favorable clinical responses. The relationship between hair indinavir concentrations and two indicators of treatment outcome, viral response and the occurrence of resistance mutations, provides strong support for the utility of hair testing in assessing exposure to antiretroviral therapies over long periods.

Although most articles on drug analysis in hair have focused on the measurement of cocaine, opiates, and amphetamines (9), interest in hair analysis for therapeutic drug monitoring has extended to anticonvulsant (10) and psychotropic (11) drugs. These drugs, like antiretroviral therapies, are given for long periods, and patient adherence influences efficacy. Measurement of antiretroviral drug levels in hair may elucidate reasons for virologic failure. This kind of long-term data can aid in interpreting self-reported adherence and may prompt pharmacokinetic studies to identify bioavailability issues or drug interactions.

For hair analysis to be useful in therapeutic monitoring, factors that influence drug levels in hair, such as age, race, extent of pigmentation and texture, cosmetic treatments, growth rate, anatomic site of hair, and physicochemical characteristics of the drug, should be considered. The extent to which a drug binds to hair depends on drug characteristics, such as affinity for lipids and charge, and on host factors. The most important host factor for drug binding seems to be melanin content. Hair consists of 0.1% to 5% melanin pigments, which are polyanion polymers attached to a protein matrix. Hair fibers with less melanin seem to take up smaller amounts of drug (12, 13); an exponential relationship is seen between hair drug levels and melanin content.

Bleaching destroys melanin and reduces drug binding, as do other hair treatments that remove melanin and alter hair structure. The reactive ingredients in cosmetic hair products can also directly degrade or modify drugs. Drug concentrations in hair can decrease by 60% to 80% after bleaching and by 20% to 40% after perming (14, 15). Dark dyes can restore the hue of hair but not the melanin, so drug uptake remains low. Because hair analysis has been used to detect drugs of abuse, attempts to use hair treatments to deliberately remove drugs have been reported. Shampooing (16) only minimally decreases drug concentrations and should not greatly affect drug testing.

Cosmetic treatment of scalp hair is increasingly prevalent among men and women, and some people are reluctant to donate scalp hair (particularly if it is of limited quantity). Thus, drug monitoring with pubic or axillary hair has been proposed. However, whereas scalp hair grows at a fairly constant rate, growth rates vary in axillary and pubic hairs and growth tends to cease after a specific length is achieved. Because the percentage of resting hairs and growth rate influence drug uptake, drug analysis using axillary or pubic hair may not be as reliable as measurements from scalp hair (17).

Drug concentrations are highest in hair at the scalp and progressively diminish along the length of the hair shaft. Therefore, the location of the hair specimen relative to the scalp should be measured during collection; optimal samples are those taken closest to the scalp. Because the growth rate of hair from the occipital scalp is less variable (18), this location is ideal for sampling; collection from underneath the top layer is optimal, as stability of drugs in hair may decrease with exposure to sunlight (19). Because drug concentration varies with the extent of pigmentation, some authors recommend adjusting drug concentrations in hair for melanin content to normalize values from individual patients (13). This adjustment provides some control for the variation introduced by race, texture, and cosmetic treatments. Finally, the anticipated development of drug analytic methods that utilize a single hair will simplify sampling and increase its acceptability to patients (20).

In conclusion, Bernard and colleagues (6) describe the relationship between the level of indinavir in hair, virologic response, and the occurrence of resistant HIV mutations. Their article provides a promising new option for monitoring exposure to antiretroviral regimens. Given the importance of long-term adherence to antiretroviral therapies for optimal outcome, hair analysis represents a significant, convenient, and affordable advance in assessing exposure to antiretroviral therapies over extended periods. Methods to control for hair pigmentation, texture, collection site, and cosmetic treatments, in addition to further study of the incorporation of individual antiretroviral drugs into hair, will help standardize this form of therapeutic monitoring and its integration into clinical care.

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LETTERS

COMMENTS AND RESPONSES

Microbiologically Confirmed Early Lyme Disease

TO THE EDITOR: Smith and colleagues (1) provided much-needed information about the characteristics of erythema migrans caused by *Borrelia burgdorferi* that will grow in Barbour–Stoenner–Kelly culture. In addition, they commented on erythema migrans–like lesions in the southeastern United States, which are associated with *Amblyomma americanum*, or lone star ticks (2), and suggested that "another agent, perhaps even from the *Borrelia* genus, may cause the infection." For this statement, they gave three references, one of which is a study by Campbell and associates that was sponsored by the U.S. Centers for Disease Control and Prevention (3).

In fact, Campbell and associates concluded quite the opposite, that is, that these tick bite–associated annular rashes were not caused by *B. burgdorferi* or related spirochetes. The state epidemiologist who initiated the study and I, as the clinician who supplied most of the patients, declined authorship because of the exclusion of relevant data and the lack of objectivity. We published our objections in the *Journal of Clinical Infectious Diseases* (4) and *Missouri Medicine* (5), including data excluded by Campbell and associates, and reiterated our opposite conclusion: that atypical *B. burgdorferi* or related spirochetes were completely compatible with data gathered in the study.

Now that increasing evidence is implicating these "Lyme-like" lone star tick–associated rashes as borreliosis, it would be a terrible mistake to give credit to Campbell and associates. In fact, on 31 March 1996, after the Campbell study's publication, Dr. David Dennis of the Centers for Disease Control and Prevention, a coauthor, was quoted in the *Kansas City Star* as saying that these rashes "could be caused by tick spit for all we know." For factual reasons, one should avoid giving credit for properly implicating borreliosis to those who actively and, in my opinion, inappropriately opposed the concept.

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IN RESPONSE: Dr. Masters objects to our inclusion of the reference by Campbell and associates (1) in our brief allusion to an erythema migrans–like rash that has been associated with the bites of lone star ticks (*Amblyomma americanum*). Although the clinical characteristics of this illness, which has been reported predominantly in the southeastern and south-central United States, have been described by Masters and colleagues (2), others, including Campbell and associates, have also contributed to the investigation of its epidemiology and possible etiology (1, 3–5). Attempts to demonstrate infection in these patients by *Borrelia burgdorferi* sensu stricto, the recognized cause of Lyme disease in the United States, have been unsuccessful. Nevertheless, as pointed out by Masters and colleagues, the characteristics of the rash and its apparent response to antibiotics suggest that this illness may be provoked by an infectious agent. The identification of "*Borrelia*-like organisms" in lone star ticks provides tantalizing circumstantial evidence that these organisms may turn out to be the cause (4, 5). Campbell and associates refer to this possibility as "intriguing and deserving of further study." Their article, although unable to provide direct evidence for a specific infectious cause for this illness, does provide a well-designed epidemiologic analysis of its occurrence in Missouri. It also describes an intense effort to search for an infectious cause. Given the wide distribution of lone star ticks in the United States, continued investigation into the clinical characteristics, epidemiology, and pathogenesis of this illness is certainly warranted.

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Resident Burnout

TO THE EDITOR: Although the articles on housestaff burnout by Shanafelt and colleagues (1, 2) and the accompanying editorial by Clever (3) present a disturbing snapshot of the mental health of trainees, they do not take important related issues into account. First, none notes that the difficult working conditions of residents are time limited. One would certainly approach the question of altering working conditions differently if residents were permanently consigned to the demands of a training environment, rather than experiencing them, as they now do, for a few years.

Second, none of the pieces addresses the potential consequences of substantial changes in the demands of residency training. Change (generally in the form of limitations on work hours) is advocated as an unalloyed good, intended to improve the life of housestaff. Even if one accepts that work changes would, in fact, boost housestaff morale, that is certainly only part of the picture.

Training programs need to concern themselves not only with the mental and physical health of their residents but also with the quality of care they ultimately provide as practicing physicians. Will physicians trained in a more nurturing environment really be better doctors? Will they provide the same level of dedication that patients have a right to expect? Will they display the very essence of professionalism, which is to put their patients' interests ahead of their own? If they are not expected to do this as trainees, how then will they learn to do it as practitioners? It is telling that Clever says "we know from experience and instinct" that more nurturing training leads to better doctoring down the line without citing any evidence to support the claim, thereby displaying the very antithesis of the evidence-based thinking and practice that we hope to instill in our trainees.

No one should support the perpetuation of difficult working conditions for residents as a professional right of passage. By the same token, no one should tamper with such conditions without considering the impact on the future practice of medicine.

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TO THE EDITOR: The report by Shanafelt and colleagues (1) and the accompanying editorial by Clever (2) demonstrate that resident burnout occurs with great frequency and may affect patient care. As Shanafelt and colleagues point out in their Table 4, these problems continue at levels unchanged over the past 15 years despite improvements in residency training, such as night float and smaller case loads. Trainees enter residency without practical knowledge yet are rapidly immersed in the care of sick patients. Worse, interns and residents change service, colleagues, and superiors every month. Medical residency is difficult and stressful.

However, although the incremental assumption of autonomy and increasingly difficult decision making is extremely stressful, it is crucial to physician development. Limiting scut work won't diminish the stressful part of residency: making tough medical decisions. Unfortunately, recent changes in residency structure already limit exposure to common conditions (3). Residency is the only time that allows trainees to see and learn for themselves what happens during the decisive, acute period of hospitalization. How can the development of this necessary skill set to care for sick patients not be stressful?

The care of patients remains a privilege, not a vocation. It is well recognized that becoming a physician is difficult. We find no false advertising denying either the rigorous training or lifestyle of physicians. Thus, we have trouble understanding why residents don't expect to feel stressed, fatigued, and challenged. The reports by Shanafelt and Collier and colleagues offer a perceptive glimpse into residency training, but we worry that the data may be driven by the most disaffected trainees. We think changes in training should be undertaken only with great care because we know that patients dislike the increasing discontinuity (5). And shouldn't they come first?

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TO THE EDITOR: Shanafelt and colleagues (1) described burnout as a syndrome of "emotional exhaustion, and a sense of low personal accomplishment that leads to decreased effectiveness at work" (1). Of the 115 residents evaluated, 76% suffered from burnout, and of these, 53% provided "at least one type of suboptimal patient care at least once monthly." Burnout was thought to lead to suboptimal patient care.

It is more likely that suboptimal patient care leads to burnout. If a person takes on a difficult task and does it well, then he tends to feel good about himself. This feeling of accomplishment generally leads to further good work. However, if a person has not been trained correctly, if he is confused about what he is doing, then he tends to develop angst, which is a setup for burnout. In other words, it is likely that the lack of appropriate training in medical school and residency lead to burnout.

Academic medicine has, over the years, been primarily interested in itself and its own interests, such as grants and publications. Clinical education has been allowed to atrophy. For example, turn to page 245 in *Cecil Textbook of Medicine*, 18th edition (2). The author writes that isotonic saline contains 140 mEq of sodium and 140 mEq of chloride. The fact is that isotonic saline in use in clinical medicine is normal saline, which contains 154 mEq of sodium and 154 mEq of chloride. How could an author contributing to a major textbook of medicine not know such a basic fact? How could the editors miss this or not know it? One can make rationalizations to explain this, but the truth may be relatively straightforward: There are far too many in academic medicine who lack competence.

I could point to other examples of errors, but suffice it to say that the level of suboptimal performance reported by Shanafelt and colleagues probably reflects the overall level of competence in academic medicine. The actions of the residents are mirroring those of their professors. The article by Shanafelt and colleagues was courageous. I hope it can serve as a basis for honest dialogue and allow us to face up to our problems in an effective manner.

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TO THE EDITOR: As Shanafelt and colleagues revealed (1), resident burnout is prevalent. Residents face long hours, sleepless nights, and heavy workloads, and they often find themselves frustrated with patient care responsibilities. The effects of this burnout, though, are not confined to a resident's personal life or attitude. As a third-year medical student rotating through clinical clerkships, I have found that the burnout inherent in residency extends beyond the residents' lives and into the sphere of medical education.

The chief resident of my gynecology rotation described the process succinctly. "As an intern, you spend your entire year lost," she explained. "During your second and third years, you become 'toxic': cynical, hardened, skeptical. Finally, during your fourth year, you start to see the light." Unfortunately, as residents travel through this process from "lost" to "toxic" to finally "seeing the light," medical students are with them for the journey. And, as a result of the close association between residents and medical education, rotating students acquire a certain "toxicity": disillusion with patient care, loss of compassion, and frustration with the demands of the current residency system.

The article by Shanafelt and colleagues addresses important concerns for the livelihood of medical residents and the resulting impact on patient care. The direct effect of resident burnout on medical students' attitudes must be evaluated, as well. Medical students learn from resident attitudes as well as from their clinical knowledge. When the medical system creates in residents attitudes aversive to effective medical care, the impact of that system extends far beyond the confines of day-to-day hospital medical practice.

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Reference

1. Shanafelt TD, Bradley KA, Wipf JE, Back AL. Burnout and self-reported patient care in an internal medicine residency program. Ann Intern Med. 2002;136:358-67. [PMID: 11874308]

IN RESPONSE: We appreciate the interest in our study of burnout in residents. Dr. Nash points out the need for caution in altering residency training and notes the lack of empirical evidence on which changes could be based. We agree that evidence is scant and view our study as an early step in establishing such an evidence base. Drs. Beckman and Fang speculate that our results disproportionately reflect a disaffected group of residents. This seems unlikely to us, since more than three quarters of the residents in the study met criteria for burnout and the participation rate was 76%. Dr. Graham suggests that burnout is a reflection of the dismal state of academic medicine, which our study did not directly address.

Although we understand that some readers may interpret our study as endorsement of changes already under way in internal medicine residencies, such as night float rotations and workload limits, we can only reiterate that our study is a cross-sectional snapshot of burnout. It does not provide longitudinal data that could lead to conclusions about the role of specific stressors or residency program features. Nor does our study provide evidence that simply reducing workload will improve physician training. A certain level of intensity may be important to developing competence in challenging situations. Research on the psychology of optimal performance indicates that maximal learning occurs when the challenge is matched to the learner's ability. Too little challenge is boring for learners; too much challenge is overwhelming (1).

We recognize that changes in residency training create new educational challenges. Improvements in residency training—with the goal of nurturing professionalism (2)—should draw on empirical evidence. Our work suggests that burnout may be an important factor in the professional development of residents. We would take Dr. Graham's call for honest dialogue one step further. We need research that will guide optimal training to develop physicians who are peak performers in every aspect: technically adept, knowledgeable, and compassionate.

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The Effect of *HFE* Genotypes on Measurements of Iron Overload

TO THE EDITOR: Since the publication of our article on the effect of genotypes on measurements of iron overload (1), we have continued our study. We present data that were gathered up to 5 September 2001 on 153 C282Y/C282Y homozygotes (79 women and 74 men) and on 31 356 white or white–Hispanic persons who were not homozygotes. In the latter group, transferrin saturation values and serum ferritin values, respectively, were available for 15 471 women and 15 204 men and for 15 009 women and 14 821 men. Sensitivities and specificities relating to these cohorts are presented in the accompanying **Table**.

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Table. **Updated Sensitivity and Specificity of Transferrin Saturation and Serum Ferritin Levels for Detection of C282Y/C282Y Homozygosity***

Substance	Cutoff Value	Sensitivity			Specificity		
		Men	Women	Both	Men	Women	Both
Transferrin saturation	≥0.45	0.8108	0.4310	0.6405 (0.5591–0.7164)	0.9428	0.9731	0.9581 (0.9558–0.9603)
	≥0.50	0.7568	0.4051	0.5752 (0.4923–0.6546)	0.9720	0.9884	0.9803 (0.9787–0.9818)
Ferritin level	≥200 ng/mL	0.7808	0.5443	0.6579 (0.5767–0.7328)	0.7568	0.9458	0.8519 (0.8478–0.8559)
	≥250 ng/mL	0.7671	0.4557	0.6053 (0.5223–0.6835)	0.8503	0.9706	0.9108 (0.9075–0.9140)

* Values in parentheses are 95% CIs.

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1. Beutler E, Felitti V, Gelbart T, Ho N. The effect of *HFE* genotypes on measurements of iron overload in patients attending a health appraisal clinic. Ann Intern Med. 2000;133:329-37. [PMID: 10979877]

Chiropractic

TO THE EDITOR: The article by Meeker and Haldeman (1) on chiropractic is highly informative on several issues but equally misleading on other points, particularly research. For instance, the authors state that there is no evidence of publication bias in the chiropractic literature. We have recently shown that, in the United Kingdom, nonpublication of severe adverse effects of chiropractic seems to be close to 100% (2). The authors also claim that 43 randomized, controlled trials of spinal manipulation for back pain have been published, but they fail to mention that most of them do not relate to chiropractic spinal manipulation.

Meeker and Haldeman state that the most recent systematic review of chiropractic for back pain, which arrived at a (partly) positive conclusion, was published in 1999 but fail to mention two systematic reviews published at the same time. One concluded that "the effectiveness of manipulation in patients with chronic pain is poorly documented" (3), while the other found "conflicting evidence on the effects of spinal manipulation in acute and chronic low back pain" (4). Similarly, the authors cite one positive study of spinal manipulation for infantile colic but do not mention a larger trial, which concluded that "chiropractic spinal manipulation is no more effective than placebo" (5). Furthermore, Meeker and Haldeman inform us that "nonserious side effects of manipulation may consist of localized discomfort, headache, or fatigue that resolves within 24 to 48 hours." However, the very study they cite in support of this statement also shows that such adverse events occur in about 50% of all patients.

This is just some of the evidence in this article that suggests biased interpretation. Readers deserve a more objective evaluation of chiropractic, which remains a highly controversial subject.

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1. Meeker WC, Haldeman S. Chiropractic: a profession at the crossroads of mainstream and alternative medicine. Ann Intern Med. 2002;136:216-27. [PMID: 11827498]
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TO THE EDITOR: After reading the article by Meeker and Haldeman (1), I have the following questions for them. First, where is the "basic science" of chiropractic? In a day and age of detailed neuroimaging by high-resolution computed tomography and magnetic resonance imaging, of neurophysiology studies and evoked potentials and electromyography, why has no one been able to demonstrate subluxations and their effects, on which chiropractic is based? Second, why doesn't chiropractic limit itself to spinal manipulation and back pain, for which there appears to be some evidence of benefit, instead of extending its reach to megavitamins, colonic irrigation, and other methods for diseases such as asthma, sinus trouble, emphysema, menopause, and psoriasis? Third, if indeed there are legitimate and ethical practitioners of chiropractic and schools that train them, why don't they speak out against chiropractic practitioners who claim that spinal manipulation and other questionable methods can treat diseases other than those restricted to the spine?

The dictionary defines quackery as "the pretension to medical skill." In my opinion, which is unchanged by Meeker and Haldeman's paper, that describes chiropractic.

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Reference

1. Meeker WC, Haldeman S. Chiropractic: a profession at the crossroads of mainstream and alternative medicine. Ann Intern Med. 2002;136:216-27. [PMID: 11827498]

TO THE EDITOR: In their paper on chiropractic (1), Meeker and Haldeman overlook one basic flaw: The chiropractic theory of vertebral subluxation and spinal manipulative adjustments is false. It is just as false today as when it was formulated more than a century ago by the founder and magic healer D.D. Palmer. A vertebral subluxation has never been demonstrated to exist and has never been shown to cause disease by theoretically interfering with neural integrity. Chiropractic has not contributed one single piece of scientific medical knowledge to prove its validity in the past 100 years. Admittedly, it has gained considerable public and political credence, but this is based only on belief and not scientific evidence. Nothing has basically changed scientifically in chiropractic since the very beginning.

I have often challenged chiropractors to name one single disease that chiropractic spinal adjustment can effectively treat, cure, improve, or prevent, along with scientific evidence to prove it, and no one has thus far been unable to do so. Claims of effective treatment of otitis media, childhood asthma, tension headaches, and even low back pain with chiropractic have all been negated by recent studies. For chiropractic to be considered scientific medical care rather than alternative unscientific care, it must first abandon the false theory of subluxations as a cause of disease and spinal adjustments as a treatment. Chiropractic colleges must stop teaching this theory and must convert to accredited medical colleges, as osteopathic schools have done, or must limit the scope of chiropractic to scientifically oriented physical therapy.

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IN RESPONSE: These letters illustrate the strong, emotional, often vitriolic responses any discussion of chiropractic evokes in certain physicians. The charge of bias cuts in many directions, as Dr. Ernst is well aware. We stand by our specific statement that overall, there is no evidence of biased reporting of randomized trials of spinal manipulation. We agree that the basic science of manipulation and of the concept of subluxation is controversial and has not yet been fully developed. However, scientists in chiropractic institutions and major universities around the world, supported by major public and private funding agencies, are making progress. Greater understanding of the theories on which manipulation is based will become available. We agree that many of the randomized trials we described were on spinal manipulation rather than specifically on chiropractic manipulation itself, but we believe that this is not a significant point. Chiropractors use all forms of manipulation. In the United States, more than 90% of all spinal manipulation services are provided by chiropractors, and research on spinal manipulation, like that on any other treatment method, is equally of value regardless of the practitioner providing it.

We elected to include only the most recent and comprehensive English-language reviews of manipulation trials out of at least 60 published in the past 25 years. The paper by Brox and colleagues to which Dr. Ernst refers is in Norwegian and does not include all trials of manipulation for chronic back pain. van Tulder, in addition, has published inconsistent conclusions (2–4). Nevertheless, 10 of 11 nationally developed practice guidelines for back pain have recommended manipulation as a treatment option (4). The trial by Olafsdottir and colleagues on infantile colic, also mentioned by Dr. Ernst, was published too late to be included in our list and does not change our already cautious conclusions.

Minor reactions to spinal manipulation are known to all practitioners and most patients of chiropractors and tend to be no more than a nuisance in practice. Patients do not seem to be concerned about these side effects. Patient satisfaction remains higher for chiropractic care than for any treatment with which chiropractic has been compared (5), and the dropout rate due to side effects in clinical trials on manipulation and chiropractic is negligible.

Chiropractic as a profession has made many advances in education, ethics, practice, and theory that give it the trappings of a mainstream health care profession, but there are still a number of claims, as pointed out by these letters, that have not been adequately evaluated. It was for this reason that we described chiropractic as a profession at the crossroads between mainstream and alternative medicine.

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East Asian Medicine

TO THE EDITOR: In the history of its interaction with the Chinese paradigm of the body, biomedicine has never started from the premise that the Chinese might have gotten something right. The anatomic paradigm has proved so strong that other paradigms have generally been dismissed as superstition or quackery. As early as the 17th century, western observers rejected Chinese readings of the body because the Chinese "did not know anatomy."

In his article on acupuncture, Kaptchuk (1) notes that the concept of qi provides a rationale for explaining change. Indeed, both Chinese philosophical systems and medicine have long focused on understanding and articulating the dynamics of change. Key terms like *qi* express the nature of process—not structures of things, but dynamic functions, in relationship.

disorder was reported 30 years ago. Since then, fewer than 50 pediatric cases have been reported, and favorable outcome in adulthood is rare.

Case Report: Our patient was born in 1973. His parents were first cousins; two of his brothers had died of infection in infancy. In the first weeks of life, the patient presented with anorexia, diarrhea, severe pancytopenia, and agammaglobulinemia. Transcobalamin II deficiency was diagnosed by the absence of TCII in serum (1). Intramuscular administration of cobalamin, 1 mg/wk, resulted in clinical and laboratory remission. Initial adherence to treatment was good, and no complications were noted during childhood. Growth and cognitive and social development were normal until adulthood.

At 20 years of age, the patient discontinued follow-up and his cobalamin injections were given at longer intervals. Eight years later, he was hospitalized with a retinal hemorrhage and otherwise normal findings on physical examination. He was pancytopenic (leukocyte count, 2.4×10^9 cells/L; granulocyte count, 0.5×10^9 cells/L; platelet count, 11×10^9 cells/L; hemoglobin level, 56 g/L), and the bone marrow was hypercellular with an increase of early erythroblasts and no excess of blast cells. Erythroblasts and proerythroblasts were megaloblastic. Intramuscular administration of 4 mg of cobalamin led to reticulocytosis, leukocytosis, and thrombocytosis within 7 days. Thereafter, oral treatment (1 mg of cobalamin daily) was tried but was followed by early relapse of pancytopenia. Long-term intramuscular cobalamin was then prescribed. The patient is now well, and his blood counts are normal.

Discussion: Few reports have described outcome of this disease in childhood (2–4). Most children have megaloblastic anemia and digestive symptoms in early infancy, which are corrected with intramuscular cobalamin. During childhood, patients may have recurrent bacterial and viral infections that are probably related to neutropenia and hypogammaglobulinemia. Impaired cognitive development and neurologic sequelae (epilepsy and gait disturbance) were observed in patients with TCII deficiency who had extended duration of illness, received inadequate cobalamin treatment, or were initially treated with folic acid instead of cobalamin (3, 4). Treatment is long-term, high-dose, intramuscular cobalamin supplementation (1 mg/wk). In some cases, oral therapy can be attempted with success (5).

This is one of the first reports of favorable long-term outcome of TCII deficiency: The neurologic condition of our patient is normal. Our findings indicate that TCII deficiency can be managed without sequelae if high-dose vitamin B_{12} supplementation is administered early and regularly.

Jean-Benoît Arlet, MD
Bruno Varet, MD
Caroline Besson, MD
Hôpital Necker
75743 Paris, France

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Correction: The Effect of *HFE* Genotypes on Measurements of Iron Overload

In an article on the relationship of iron measurements to hemochromatosis genotypes (1), some errors in the calculation of the specificity of transferrin saturation measurements were presented in Table 5. Corrected data are given in the current Table.

Reference

1. Beutler E, Felitti V, Gelbart T, Ho N. The effect of *HFE* genotypes on measurements of iron overload in patients attending a health appraisal clinic. Ann Intern Med. 2000;133:329-37. [PMID: 10979877]

Table. **Corrected Values for Specificity of Transferrin Saturation and Serum Ferritin Level for Detection of C282Y/C282Y Homozygosity***

Substance	Cutoff Value	Specificity		
		Men	Women	Both
Transferrin saturation	≥0.45	0.9442	0.9755	0.9596 (0.9550–0.9640)
	≥0.50	0.9757	0.9904	0.9830 (0.9798–0.9858)
Ferritin level	≥200 ng/mL	0.7826	0.9438	0.8596 (0.8515–0.8673)
	≥250 ng/mL	0.8660	0.9668	0.9141 (0.9076–0.9203)

* Values in parentheses are 95% CIs.

MEDICAL WRITINGS

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. Order phone numbers and Web sites can be used to place orders directly with publishers.

Primary Care Medicine Recommendations for PDA [CD-ROM]

Goroll AH and Mulley AG. Philadelphia: Lippincott Williams & Wilkins; 2002. $49.95. ISBN 0781734908. Order at www.lww.com.

Field of medicine: Primary care.

Format: CD-ROM.

System requirements: Handheld devices with Palm, Windows CE, or Windows Pocket PC operating system. Uses 899 K of memory.

Audience: Primary care providers.

Purpose: To provide a practical reference for primary care.

Content: *Primary Care Medicine Recommendations* (*PCMR*) is a PDA port of Goroll and Mulley's book, *Primary Care Medicine Recommendations* (Lippincott Williams & Wilkins, 2001); both are companions to the well-known book, *Primary Care Medicine: Office Evaluation and Management of the Adult Patient* (Lippincott Williams & Wilkins, 2000).

Usability: Installation is easy. After opening the diabetes section, I made seven screen taps, mostly to scroll down, to find the indications for angiotensin-converting enzyme (ACE) inhibitors.

Highlights: Reasonably friendly and broad coverage of primary care. Ability to link to other SkyScape products, such as the Washington Manual and 5 Minute Clinical Consult. The bibliography at the end of each section directs the user to the print or Web version at www.lwwmedicine.com, which provides references to the content and also a weekly updating service.

Limitations: The method of updating is not stated. An additional subscription is required to access the Web site. I also compared *PCMR* with selected content from Mincey's "Update in General Internal Medicine" (Ann Intern Med. 2001;135:300-1), which reviewed articles published in 2000. *PCMR* well reflected basic issues, such as using diuretics as first-line therapy for hypertension. However, PCMR did not reflect more subtle issues, such as deciding which populations to treat with ACE inhibitors on the basis of Heart Outcomes and Prevention in the Elderly (HOPE) study or the use of hip protectors to reduce hip fractures in the elderly.

Related products: There are other related Lippincott Williams & Wilkins PDA products. In addition, there are competing PDA products with stated methods of updating content that will be available in the future from UpToDate (www.UpToDate.com) and PIER (http://pier.acponline.org).

Reviewer: Robert Badgett, MD, Associate Editor for Electronic Publication, *Annals of Internal Medicine*; University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Conflict of interests: I have previously worked with UpToDate and currently work for ACP–ASIM (publisher of PIER).

Clinical Management of Chronic Obstructive Pulmonary Disease

Similowski T, Whitelaw WA, and Derenne JP, eds. 1072 pages. New York: Marcel Dekker; 2002. $250.00. ISBN 0824706102. Order phone 212-696-9000.

Field of medicine: Pulmonary medicine.

Format: Hardcover book.

Audience: Pulmonary specialists, internal medicine physicians, or general practitioners with a desire for a comprehensive knowledge of management of chronic obstructive pulmonary disease (COPD).

Purpose: To inform the clinician on current COPD management, including several chapters providing an international perspective.

Content: Multiauthored book comprising 45 chapters. The first chapter, by Snider, gives a panoramic view on what we have learned about COPD and where the future challenges lie with this complex disorder. The next eight chapters review diagnostic evaluation with assessments of dyspnea, quality of life, and disability. The core of the text provides specific information on the pathophysiologic and pharmacologic treatment of airway, vascular, and infectious problems in COPD. There are prominent sections related to associated conditions, such as anxiety, depression, left- and right-sided heart failure, and sleep disorders. Discussions of appropriate nutrition, rehabilitation, and the role of respiratory muscles and their training during physiotherapy are included. Long-term oxygen therapy, domiciliary noninvasive ventilator support, and tracheostomy management are also well covered.

Highlights: The authors are widely recognized authorities. The references are thorough and extensive. The chapters by Snider and Barnes give an excellent review of the past and an exciting glimpse of future COPD management.

Limitations: Evidence-based medicine in COPD is developing and dynamic; recommendations are changing and often are not totally supported. However, the chapters are as up to date as possible given the time constraints of a major publication. The excellent chapter by Verlott has a "past submission addendum" with some of the more recent evidence supporting steroids in stable COPD, but this chapter is still not up to date.

Related reading: Bourbeau and colleagues' *Comprehensive Management of Chronic Obstructive Pulmonary Disease* (BC Decker, 2002) presents a unique multidisciplinary team approach with a goal toward improving patient self-management and disease control. Voelkel and MacNee's *Chronic Obstructive Lung Diseases* (BC Decker, 2001) complements the reviewed text by focusing on the processes that destroy the lung.

Reviewer: Warren Summer, MD, Lousiana State University Health Science Center, New Orleans, Louisiana.

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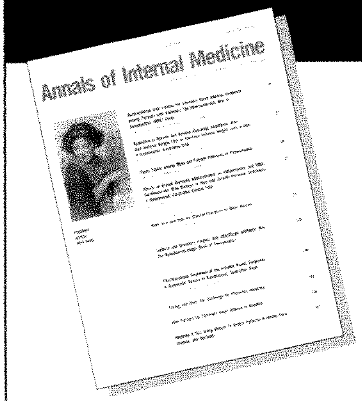

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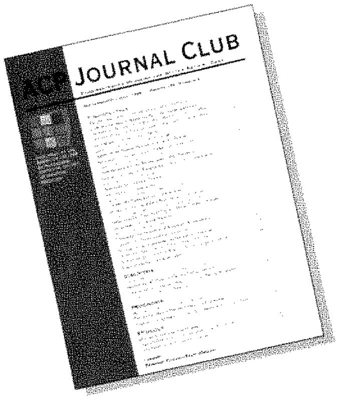

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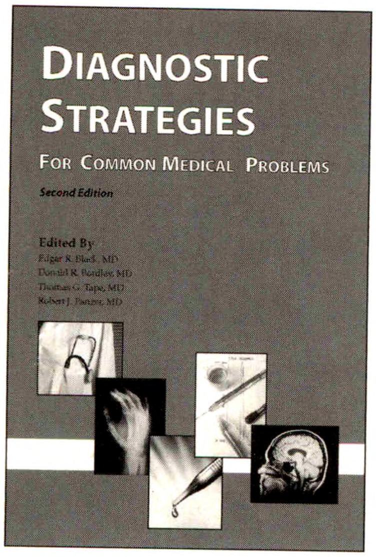

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ASIM

YOUR PATIENT:

A 45-year-old woman presents with weight loss of approximately 9 kg (20 lb) over the past 12 months. She has been aware of no change in appetite. She eats three meals daily and snacks most evenings. Her activity has similarly been unchanged. She exercises by walking 2 to 3 miles three or four times weekly. She takes no medication and reports no alcohol or drug use. Review of systems reveals a 1- to 1.5-year history of a pruritic rash on the trunk and extremities. She reports occasional vague abdominal pain and bloating, which subside spontaneously in a few hours, and notes the passage of flatus. She has no food intolerance, difficulty swallowing, sweating, tremor, constipation, diarrhea, or arthritis. She has normal, regular menstrual periods and has two to three stools per day, with no recent change.

The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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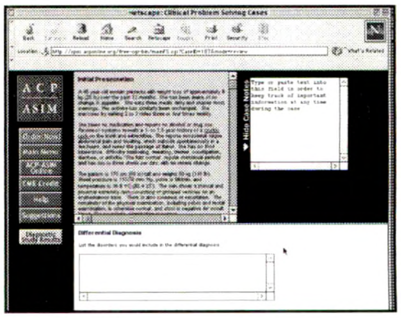

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ARTICLES

Regular Mammography Use Is Associated with Elimination of Age-Related Disparities in Size and Stage of Breast Cancer at Diagnosis 783

W.M. Randolph, J.S. Goodwin, J.D. Mahnken, and J.L. Freeman

There is little evidence or consensus about mammography for women age 75 years and older. Compared with women 69 to 74 years of age, they have mammography less frequently and have larger tumors and more advanced stage at diagnosis. This study found that breast cancers in older women who had mammography were similar in size and stage to breast cancers in women 69 to 74 years of age.

Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections 791

N.D. Friedman, K.S. Kaye, J.E. Stout, S.A. McGarry, S.L. Trivette, J.P. Briggs, W. Lamm, C. Clark, J. MacFarquhar, A.L. Walton, L.B. Reller, and D.J. Sexton

The authors define health care–associated bloodstream infections as those that are associated with intensive, out-of-hospital care of serious illness. These bloodstream infections are similar to nosocomial infections, but different from community-acquired infections, in the frequency of comorbid conditions, source of infection, pathogens and their susceptibility patterns, and mortality rate. This new category has important implications for the choice of empirical therapy and infection control surveillance.

Use of Postmenopausal Hormones, Alcohol, and Risk for Invasive Breast Cancer 798

W.Y. Chen, G.A. Colditz, B. Rosner, S.E. Hankinson, D.J. Hunter, J.E. Manson, M.J. Stampfer, W.C. Willett, and F.E. Speizer

Both alcohol consumption and postmenopausal hormone use were associated with an increased incidence of breast cancer. Physicians should counsel women who are currently taking postmenopausal hormone therapy to consider the added risks of regular alcohol consumption.

ACADEMIA AND CLINIC

Complementary and Alternative Medicine for Menopausal Symptoms: A Review of Randomized, Controlled Trials 805

F. Kronenberg and A. Fugh-Berman

Black cohosh and foods that contain phytoestrogens show promise for the treatment of menopausal symptoms. Clinical trials do not support the use of other herbs or complementary and alternative medical therapies. Long-term safety data on individual isoflavones or isoflavone concentrates are not available.

UPDATE

Update in Hospital Medicine 814

B.E. Flansbaum and J.M. Huddleston

This Update summarizes articles that are important to primary inpatient physicians. The selected articles cover quality improvement, invasive procedures, pulmonary diseases, infectious diseases, cardiology, endocrinology, and critical care.

PERSPECTIVE

Prevention of Plaque Rupture: A New Paradigm of Therapy 823

J.S. Forrester

The author describes the steps in plaque destabilization and links them to a set of clinical strategies that may substantially decrease the incidence of acute coronary syndromes.

CLINICAL GUIDELINES

Postmenopausal Hormone Replacement Therapy for Primary Prevention of Chronic Conditions: Recommendations and Rationale 834

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. It concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache 840

V. Snow, K. Weiss, E.M. Wall, and C. Mottur-Pilson, for the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine

This guideline, developed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine, with assistance from the American Headache Society, applies to patients with acute migraine attacks, with or without aura, and patients with migraine who are candidates for preventive drug therapy.

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EDITORIAL

Health Care–Associated Bloodstream Infections: A Change in Thinking 850

R. Gaynes

The study by Friedman and colleagues in this issue presents an important clinical message—that clinicians should reconsider therapy for patients with community-acquired bloodstream infections if they have recently received intensive, out-of-hospital care for serious illness.

ON BEING A PATIENT

Şanti 852

J.K. Rao and V.R. Koppaka

"You should just be his children and not doctors," we were advised early on. The patients were managed according to protocols while the surgeons operated. "Surgical attendings just don't have time to talk to families," the nurses explained, apologetically. This was a system that worked, usually.

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Annals of Internal Medicine | ARTICLE

Regular Mammography Use Is Associated with Elimination of Age-Related Disparities in Size and Stage of Breast Cancer at Diagnosis

Whitney M. Randolph, PhD; James S. Goodwin, MD; Jonathan D. Mahnken, MS; and Jean L. Freeman, PhD

Background: There is little consensus about recommending mammography for women 75 years of age and older. These women have mammography less frequently and are more likely to receive a diagnosis of advanced breast cancer.

Objective: To examine the relationship between use of screening mammography and size and stage of cancer at diagnosis in older women.

Design: Retrospective cohort study.

Setting: Tumor registries in the Surveillance, Epidemiology, and End Results (SEER) program.

Patients: 12 038 women who were Medicare beneficiaries, were at least 69 years of age, resided in a SEER area, and received a new diagnosis of breast cancer in 1995 through 1996.

Measurements: Screening mammograms obtained in the 2 years before breast cancer diagnosis (none, one, or at least two) and stage and size of tumor at diagnosis.

Results: Older women (≥75 years of age) had larger tumors at diagnosis and were less likely to have undergone screening mammography than younger women (69 to 74 years of age). The association between increased mammography use and smaller tumor size and stage was significantly greater in older women than in younger women ($P = 0.010$ for stage; $P = 0.001$ for size). The percentage of regular mammography users who received a diagnosis of high-stage disease (28% vs. 26%; $P > 0.2$) and the mean size of the tumors (15.0 mm vs. 15.1 mm; $P > 0.2$) did not significantly differ between younger and older women, respectively. These findings remained constant after controlling for factors that might contribute to biases.

Conclusion: Mammography in older women is associated with elimination of age-related disparities in size and stage of breast cancer at diagnosis.

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Among U.S. women, breast cancer is the most common type of cancer and is the second leading cause of cancer-related death (1, 2). Incidence of breast cancer increases with age; the highest incidence (483.3 per 100 000 women) is in women 75 to 79 years of age (2). Breast cancer tends to be found at more advanced stages and with larger tumor sizes in older women, which contributes to documented poorer survival (2–6).

Although older women are more vulnerable to breast cancer, they are less likely to use screening mammography (7–15). Part of what may be contributing to the low mammography screening rates in women 65 years of age and older is lack of consensus about the screening interval and when to stop screening in this age group. Screening mammography has been found to significantly reduce breast cancer mortality rates in clinical trials of women 50 to 69 years of age (16–21), and the benefits may extend to women 70 to 74 years of age (22, 23). The American Cancer Society and the National Cancer Institute recommend annual mammography with no upper age limit (1, 2, 4), while the American Geriatrics Society recommends screening every 1 to 2 years up to age 75 years and every 2 to 3 years thereafter for women with an estimated life expectancy of at least 4 years (24). The U.S. Preventive Services Task Force recently revised its breast cancer screening guidelines and now recommends routine screening mammography (every 1 to 2 years) for all women 40 years of age and older (25).

We sought to assess the potential value of screening mammography in older women by determining how the frequency of screening is related to tumor size and stage at diagnosis. Specifically, we hypothesized that higher disease stage at diagnosis would not be found in older women who undergo regular mammography.

METHODS

Data Source

Data on screening use and tumor characteristics were obtained from a database of linked cancer registry records from the Surveillance, Epidemiology, and End Results (SEER) program and Medicare claims from the Centers for Medicare & Medicaid Services (2, 26, 27). This database contains information on persons 65 years of age and older who received a diagnosis of any cancer (except nonmelanoma skin cancer) from 1973 through 1996 in one of the SEER areas and who were linked to the Medicare enrollment file (93.8% linkage rate). The SEER data used in this study include each patient's sociodemographic characteristics, diagnosis date, and tumor size and stage at diagnosis. Linked Medicare data for the study include claims extracted from three Medicare files over the period 1991 to 1996: the Medicare Provider Analysis and Review file (hospital inpatient and skilled nursing home stays), the National Claims History 100% Physician/Supplier data file (physician and other medical services), and the Hospital Outpatient Standard Analytic File (hospital outpatient services) (28). In addition to the SEER cases and their Medi-

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Context

Women older than 75 years of age use mammography less frequently than younger women and more frequently have advanced-stage breast cancer at diagnosis. The effectiveness of screening mammography after age 75 years is unknown.

Contribution

These researchers used data from the Surveillance, Epidemiology, and End Results program to explore the relationship between previous mammography in older women and size and stage of breast cancer at diagnosis. Older and younger women who used mammography had tumors that were of similar size and stage at diagnosis.

Implications

Mammography use after age 75 years leads to earlier detection of tumors. This study does not tell us whether screening women after age 75 years improves breast cancer mortality rates.

–The Editors

care claims, the linkage project provided claims data for a 5% sample of SEER patients with another type of cancer and a 5% control sample of patients in SEER areas who did not have cancer. These data were used to compute the denominators (number of breast cancer cases, non–breast cancer cases, and noncancer controls) for cancer incidence rates.

Patients

Our study sample consisted of all women in the SEER registries who received a diagnosis of incident breast cancer in 1995 or 1996 and were linked with the Medicare data. Since our method for measuring mammography use required 4 years of claims data before diagnosis, we limited the study to women who were 69 years of age or older on 1 January of the year of their diagnosis, were enrolled in Medicare Parts A and B on the month of their diagnosis and for the 4 previous years, and were not members of a health maintenance organization at any time during those 49 months. Women not meeting these criteria were excluded because their claims for mammography and other medical services may have been incomplete.

A total of 16 498 women age 69 years or older received a diagnosis of incident breast cancer from 1995 through 1996. Of these, 1047 were excluded for lack of Parts A and B coverage. An additional 3413 women were excluded because of membership in a health maintenance organization, resulting in 12 038 eligible women. Approximately 37% of the eligible women were 69 to 74 years of age, 28% were 75 to 79 years of age, and 34% were 80 years of age and older. Data were available on tumor size for 10 335 patients and on stage for 11 039 patients.

Measures

Tumor size was a continuous variable, measured in millimeters. Tumors larger than 100 mm ($n = 43$) and inflammatory cancer ($n = 96$) were recoded as 110 mm. Stage at diagnosis was measured by using the American Joint Committee on Cancer staging classification, which was used to identify patients who received a diagnosis of low-stage (in situ or stage I) or high-stage (stage IIa and greater) breast cancer.

We defined use of screening mammography on the basis of the number of screening mammograms in the 24 months before diagnosis of breast cancer. Nonusers had no screening mammograms, single users had at least one screening mammogram, and regular users had two or more screening mammograms obtained at least 11 months apart. Since the procedure codes on the claims distinguish poorly between screening and diagnostic mammography (14, 29, 30), we defined a screening mammogram as a bilateral mammogram (physician claim with a Current Procedure Terminology [CPT] code of 76091 or 76092) with no evidence in any of the patient's claims files of either 1) a previous mammogram (CPT codes 76090, 76091, 76092) performed within 11 months or 2) a breast mass or breast cancer diagnosis (International Classification of Diseases, 9th revision, Clinical Modification codes 174xx, 2330, 61172) in the 2 years before the current diagnosis. In addition, for mammography claims with a screening CPT code (76092), a screening diagnosis code of V16.3, V10.3, V72.5, or V1589 (International Classification of Diseases, 9th revision, Clinical Modification) needed to be present.

Information on sociodemographic characteristics was obtained from the linked SEER–Medicare database and was used to categorize patients by age at diagnosis (69 to 74 years or ≥75 years), marital status (currently married or currently not married), and race–ethnicity (white, African American, Hispanic, or other). Socioeconomic status was defined as the median household income of the patient's census tract. Comorbidity was measured by using an adaptation of the Charlson Comorbidity Index (31, 32) that was developed by Klabunde and colleagues (33) for Medicare claims data.

Statistical Analysis

We used likelihood ratio chi-square statistics to compare socioeconomic characteristics, level of comorbidity, mammography use, and stage at diagnosis in patients 69 to 74 years of age and those 75 years of age and older. Logistic regression was then used to test for the effect on disease stage (low vs. high) of mammography use, age and the interaction of mammography use, and age, controlling for census tract income, marital status, SEER region, race–ethnicity, and comorbid conditions. The effect of the interaction of mammography use and age on stage was evaluated with appropriate comparisons of the regression coefficients, corresponding to the two age groups within the three types of mammography users (nonuser, single user, and regular user). The fit of this model was tested by using the Hosmer–Lemeshow goodness-of-fit statistic (34). In a similar manner, we used analysis of variance to examine the effect of mammography use, age, and their interaction on the size of tumors at diagnosis. Lack of fit for this model was tested by separating the error sum of squares into that due to pure error and that due to lack of fit. The ratio of these two sums of squares (each divided by their corresponding degrees of freedom) yields an *F*-test for the fit of the model (35). We were able to use this method because our data contained replication, or covariate patterns that contained more than one observation. **Appendix Tables 1, 2, and 3**, available at www.annals.org, show the parameter estimates and confidence intervals corresponding to the logistic (stage) and ordinary least-squares (size) regression models. All computations and data management were performed by using SAS software, version 8.1 (SAS Institute, Inc., Cary, North Carolina) (36).

Table 1. **Characteristics of the Study Sample***

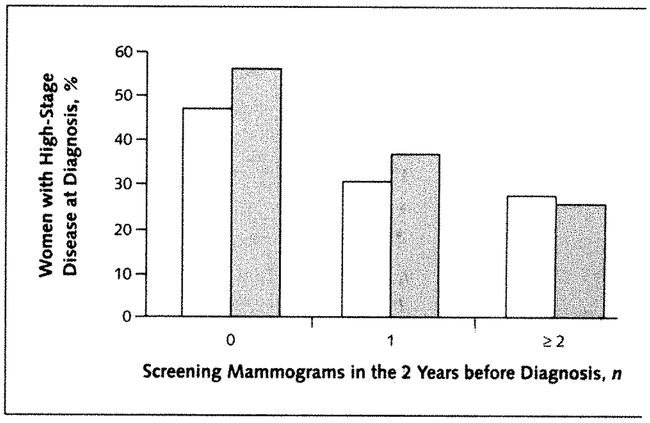
Characteristic	Women 69–74 Years of Age†	Women ≥75 Years of Age	All Women
	←———	*n (%)*	———→
AJCC stage at diagnosis			
Ductal carcinoma in situ	623 (15)	675 (10)	1298 (12)
I	2084 (49)	3167 (46)	5251 (48)
IIA	815 (19)	1547 (23)	2362 (21)
IIB	310 (7)	571 (8)	881 (8)
II, NOS	24 (1)	50 (1)	74 (1)
IIIA	104 (2)	182 (3)	286 (3)
IIIB	90 (2)	261 (4)	351 (3)
IV	176 (4)	360 (5)	536 (5)
Race/ethnicity			
White, non-Hispanic	3644 (87)	6018 (89)	9662 (88)
African American	247 (6)	401 (6)	648 (6)
White Hispanic	137 (3)	184 (3)	321 (3)
Other	146 (4)	146 (2)	292 (3)
Screening mammography‡			
Nonuser	1397 (33)	2799 (41)	4196 (38)
Single user	2272 (54)	3359 (49)	5631 (51)
Regular user	557 (13)	655 (10)	1212 (11)
Marital status			
Married	2152 (52)	2077 (31)	4229 (39)
Not currently married	1974 (48)	4545 (69)	6519 (61)
Median annual income			
<\$25 000	296 (7)	578 (9)	874 (8)
≥\$25 000	3740 (93)	5895 (91)	9635 (92)
Comorbidity score			
≤1	3498 (83)	5242 (77)	8740 (79)
>1	728 (17)	1571 (23)	2299 (21)

* Women 69 to 74 years of age and women at least 75 years of age differed significantly in prevalence of all characteristics ($P \leq 0.001$ for all characteristics except median income, for which $P = 0.004$). All comparisons were performed by using the likelihood ratio chi-square test. Race/ethnicity was unknown or missing for 116 women, marital status was unknown or missing for 291 women, and median income was missing for 530 women. AJCC = American Joint Committee on Cancer; NOS = not otherwise specified.

† Age started at 69 years so that 4 years of previous Medicare claims data would be available for each woman in the sample.

‡ Nonuser = no screening mammograms in the 2 years before diagnosis; single user = one screening mammogram in the 2 years before diagnosis; regular user = at least two screening mammograms obtained at least 11 months apart.

Figure. **Percentage of women with high-stage disease (stage IIA or higher at diagnosis), stratified by mammography use and age.**



White bars indicate women 69 to 74 years of age; shaded bars represent women at least 75 years of age.

Role of the Funding Sources

The funding sources had no role in the analysis or interpretation of the study findings. The final manuscript was reviewed by the U.S. National Cancer Institute and the Centers for Medicare & Medicaid Services to ensure the confidentiality of patients and providers in the SEER areas.

RESULTS

Table 1 presents the characteristics of the 11 039 women age 69 years or older for whom data on stage were available and who received a diagnosis of breast cancer in 1995 through 1996, stratified by age. Women 75 years of age or older were more likely to receive a diagnosis of advanced disease than were women 69 to 74 years of age. For example, 44% of women 75 years of age or older received a diagnosis of stage IIa disease or worse compared with 36% of women 69 to 74 years of age ($P < 0.001$). Women 75 years of age and older were also significantly less likely to be regular users of mammography, that is, to have had at least two screening mammograms obtained at least 11 months apart in the 2 years before diagnosis ($P < 0.001$). A higher percentage of older women also had no screening mammograms in the 2 years before diagnosis (41% vs. 33%; $P < 0.001$).

Overall, 41% of the women in the sample received a diagnosis of high-stage (stage IIa or worse) cancer. Fifty-three percent of the women with no screening mammograms in the 2 years before diagnosis had high-stage disease (stage IIa or worse), while 34% of the women with only one screening mammogram and 27% of the women with two or more screening mammograms had high-stage cancer ($P < 0.001$). We examined whether use of mammography is associated with a change in the previously documented relationship between advanced age and increased likelihood of high-stage disease. The **Figure** shows the per-

Table 2. **Mean Size of Tumor at Diagnosis**

Previous Use of Screening Mammography*	Mean Tumor Size in Women 69–74 Years of Age†	Mean Tumor Size in Women ≥75 Years of Age†	Adjusted Mean Tumor Size in Women 69–74 Years of Age‡	Adjusted Mean Tumor Size in Women ≥75 Years of Age‡
	←		*mm*	→
Nonuser	23.8	27.9	25.5	28.9
Single user	17.2	19.0	19.3	20.6
Regular user	15.0	15.1	17.4	16.9

* Nonuser = no screening mammography in the 2 years before diagnosis; single user = one screening mammogram in the 2 years before diagnosis; regular user = at least two screening mammograms obtained at least 11 months apart. For nonusers 69 to 74 years of age vs. nonusers at least 75 years of age, $P < 0.001$ (unadjusted and adjusted). For single users 69 to 74 years of age vs. single users at least 75 years of age, $P < 0.001$ (unadjusted) and $P = 0.012$ (adjusted). For regular users 69 to 74 years of age vs. regular users at least 75 years of age, $P > 0.2$ (unadjusted and adjusted).

† Generated by adding the appropriate coefficients from an ordinary least-squares regression model for the main effects of age, previous mammography use, and their interaction.

‡ Based on a sample of 9530 women. Along with age and previous screening, the following were included in the model: race/ethnicity; Surveillance, Epidemiology, and End Results area; marital status; median household income; and comorbid conditions.

centage of women who received a diagnosis of high-stage disease according to previous mammography use and age at diagnosis. Age differences in these percentages varied significantly by previous mammography use ($P = 0.010$). High-stage disease was diagnosed in 47% of younger women and 56% of older women who had no screening mammograms in the 2 years before diagnosis and in 31% of younger women and 37% of older women who had only one ($P < 0.001$ for both comparisons). However, among women with two or more screening mammograms in the 2 years before diagnosis, diagnosis of high-stage disease did not significantly differ between younger and older women (28% vs. 26%; $P > 0.2$). In a multivariate analysis controlling for ethnicity, marital status, SEER area, income, and comorbid conditions, age and previous mammography use had a significant effect on likelihood of high-stage disease at diagnosis ($P = 0.009$); mammography use had a stronger effect on stage at diagnosis among older women.

We conducted similar analyses on women for whom information on tumor size was available ($n = 10\,335$). The mean tumor size for the entire sample (±SD) was 21.1 ± 18.6 mm. Tumor size was smallest among women with two or more screening mammograms in the 2 years before diagnosis (15.0 ± 12.4 mm). In comparison, women who had one screening mammogram in the 2 years before diagnosis had larger tumors (18.3 ± 14.9 mm) and those who had no screening mammograms had the largest tumors (26.6 ± 22.8 mm) ($P < 0.001$).

Table 2 shows the mean tumor size stratified by age group and previous use of screening mammography and adjusted for other patient characteristics. There was a significant interaction of screening mammography use and age on tumor size ($P = 0.001$). The decrease in tumor size associated with mammography use was greater in women 75 years of age and older than for those 69 to 74 years of age ($P = 0.005$ for women with one screening mammogram and $P = 0.002$ for women with two screening mammograms). As a result of this interaction between age and mammography use, tumor size was approximately the same for older and younger women who had two screening mammograms in the 2 years before diagnosis (15.1 mm vs. 15.0 mm; $P > 0.2$).

Observational studies of mammography effectiveness are subject to certain biases that tend to inflate estimates of potential benefits from a screening test (37). In the case of screening mammography, less aggressive, slower-growing tumors might be more likely to be detected by mammography (length bias); more cases of ductal carcinoma in situ that would not necessarily evolve into life-threatening cancer might be diagnosed (overdiagnosis); and women who undergo regular screening mammography might be more likely to have regular examinations by a physician and thus be more likely to have cancer diagnosed early (selection bias).

We took several approaches to examine the effect of these biases and to control for them. First, to explore length bias, we analyzed the histologic grade of tumors in the regular mammography versus nonmammography groups. Compared with women who had no screening mammograms in the 2 years before the diagnosis of breast cancer, women with two or more screening mammograms were significantly more likely to have a well or moderately differentiated tumor, as designated by histologic grade (70% vs. 62%; $P < 0.001$).

Second, to explore the effect of overdiagnosis, we examined the association of previous screening mammography on the odds of receiving a diagnosis of ductal carcinoma in situ. Women with two or more screening mammograms in the 2 years before diagnosis were significantly more likely to receive a diagnosis of ductal carcinoma in situ than were women with no screening mammograms (18% vs. 9%; $P < 0.001$).

Third, to explore selection bias, we examined whether women who received regular screening mammography were more likely to have frequent contacts with physicians. The mean number of physician visits differed significantly across age groups ($P < 0.001$). Women 69 to 74 years of age with two or more screening mammograms in the 2 years before diagnosis (regular users) had on average 2.8 more visits per year than women with no screening mammograms (nonusers). The difference was approximately 2.5 visits for women 75 years of age and older.

To control for these potential biases, we repeated the analyses in **Table 2** after excluding patients with ductal carcinoma in situ and controlling for histologic grade at diagnosis and number of physician contacts (Table 3). The pattern of the relationships between tumor size, patient age, and previous use of screening mammography is similar to those found in Table 2. The interaction between age and mammography use was significant ($P = 0.015$); screening mammography had more effect on tumor size in the older age group (Table 3).

Table 4 presents the stage-specific rates of breast cancer incidence for nonusers of mammography versus regular users. Compared with nonusers, women 69 to 74 years of age and those 75 years of age and older who underwent regular mammography had a higher incidence of early-stage cancer and a lower incidence of later-stage cancer.

DISCUSSION

Our data suggest that the beneficial effects of regular screening mammography on size and stage of tumors at diagnosis extend to women 75 years of age and older. Indeed, the association between mammography use and size and stage was actually greater in women 75 years of age and older than in women age 69 to 74 years. Among women who had no screening mammograms in the 2 years before diagnosis, those who were 75 years of age and older had larger tumors and higher-stage disease than women 69 to 74 years of age. However, among women who had two or more screening mammograms in the 2 years before diagnosis, those who were 75 years of age and older had virtually the same size tumors and were as likely to have high-stage disease as women 69 to 74 years of age.

Evidence-based medicine is grounded in randomized, controlled trials. However, no trial has reported results of mammography in women older than 74 years of age, and it is unlikely that such a trial will be performed in the future. This lack of data on efficacy of mammography in older women has resulted in uncertainty among clinicians and inconsistency among different mammography guidelines produced by professional organizations and consensus panels (1, 24, 25). In lieu of data on efficacy from controlled trials, important information can be obtained from other sources, such as decision analyses and population-based effectiveness studies. Several recent studies using these approaches have provided evidence that regular screening mammography is useful in women 75 years of age and older.

Using a decision analysis model to assess the utility of breast cancer screening for older women, Mandelblatt and coworkers (38) concluded that screening mammography was potentially beneficial even for women in their 80s. McCarthy and associates (39) examined older women who received a diagnosis of breast cancer from 1987 to 1993 in three SEER areas (Atlanta, Georgia; Connecticut; and Seattle, Washington) and reported that nonusers of mammography were three times more likely to receive a diagnosis of high-stage breast cancer than were regular users. Smith-Bindman and colleagues (40), in a retrospective cohort study of 6767 women 66 to 79 years of age, reported that risk for metastatic disease at diagnosis was 43% lower in screened women. Our results confirm that regular mammography use is associated with earlier-stage disease in older women. We extend earlier findings to show that regular mammography use is associated with elimination of age-related disparities in size and stage of breast cancer at diagnosis. Our findings were not affected by adjustment for factors that might contribute to overdiagnosis or selection or length biases.

Our results should be interpreted with an understanding of the extent to which the classic screening biases may have affected the findings. In particular, the observed effect of mammography use on size and stage of tumor—both within and across age groups—may be influenced by differences in access to care (selection bias), prognostic selection (length bias), and the number of cancer cases diagnosed in situ (overdiagnosis). These biases, in addition to lead-time bias, could also influence the relationship between use of screening mammography and other outcomes, such as quality of life and survival from breast cancer, which we did not address.

To evaluate the effect of overdiagnosis and length and selection bias, we generated statistical models of tumor size and stage that excluded women with ductal carcinoma in situ and adjusted for pathologic grade and number of phy-

Table 3. **Mean Size of Tumors at Diagnosis in Women without Ductal Carcinoma in Situ**

Previous Use of Screening Mammography*	Mean Tumor Size in Women 69–74 Years of Age†	Mean Tumor Size in Women ≥75 Years of Age†	Adjusted Mean Tumor Size in Women 69–74 Years of Age‡	Adjusted Mean Tumor Size in Women ≥75 Years of Age‡
	←	mm		→
Nonuser	23.8	27.9	30.3	33.4
Single user	17.2	19.0	24.3	25.5
Regular user	15.0	15.1	23.0	22.7

* Nonuser = no screening mammograms in the 2 years before diagnosis; single user = one screening mammogram in the 2 years before diagnosis; regular user = at least two screening mammograms obtained at least 11 months apart. For nonusers 69 to 74 years of age vs. nonusers at least 75 years of age, $P < 0.001$ (unadjusted and adjusted). For single users 69 to 74 years of age vs. single users at least 75 years of age, $P < 0.001$ (unadjusted) and $P = 0.019$ (adjusted). For regular users 69 to 74 years of age vs. regular users at least 75 years of age, $P > 0.2$ (unadjusted and adjusted).

† Generated by adding the appropriate coefficients from an ordinary least-squares regression model for the main effects of age, previous mammography use, and their interaction.

‡ Based on a sample of 8805 women. Along with age and previous screening, the following were included in the model: race/ethnicity; Surveillance, Epidemiology, and End Results area; marital status; median household income; comorbid conditions; grade of tumor; and number of physician visits.

Table 4. **Incidence of Breast Cancer in 1995–1996***

Disease Stage at Diagnosis	Annual Breast Cancer Incidence in Regular Mammography Users		Annual Breast Cancer Incidence in Nonusers	
	69–74 Years of Age	≥75 Years of Age	69–74 Years of Age	≥75 Years of Age
	n/10 000 women			
Ductal carcinoma in situ	14.0	15.4	3.8	2.3
I	36.7	55.1	13.1	10.7
II	17.5	21.4	9.9	10.8
III	1.1	2.3	2.6	3.0
IV	0.8	0.9	2.7	2.8
All stages	69.8	94.6	32.1	29.5

* Incidence rates were computed by using the number of breast cancer cases in the categories of screening use and age and the two 5% samples of women with cancer other than breast cancer and cancer-free controls. Numerators for the rates were the number of breast cancer cases, by stage, during 1995–1996 in each of the categories of age and screening use. The corresponding denominators were sums of the number of breast cancer cases added to 20 times the number of non–breast cancer cases in the Surveillance, Epidemiology, and End Results program plus 20 times the number of noncancer controls in each category of age and screening use.

sician visits in the predisease period. Adjustment for these biases reduced the difference in mean tumor size between women age 69 to 74 years and women age 75 years and older who had not had previous screening mammography (from 3.4 mm to 3.1 mm). While this 3.1-mm difference in size remains highly statistically significant, its clinical significance could reasonably be questioned. In other words, how important is a 3.1-mm difference in size at diagnosis to prognosis? To address that issue, we performed a survival analysis of all women age 65 years and older who received a diagnosis of breast cancer between 1988 and 1993 in the SEER registry as a function of tumor size at diagnosis, controlling for age and SEER site. Each 1-mm increase in size at diagnosis was associated with a 0.8% increase in breast cancer death during 5 years of follow-up (hazard ratio, 1.008 [95% CI, 1.007 to 1.008]). Thus, a 3.1-mm increase in tumor size at diagnosis would be associated with an approximate 2.5% increase in breast cancer mortality rate.

Consistent with the effect of previous mammography use on stage at diagnosis, there was a shift in stage-specific incidence rates among regular mammography users compared with nonusers; regular users had higher rates of stage I and II disease and lower rates of stage III and IV disease. As expected, the overall incidence of breast cancer was considerably higher in the women who had regular mammography (**Table 4**).

Similar findings were reported in controlled trials of screening mammography (41, 42). For example, in the Swedish Two-County Trial (43), the rate of cancer detection was approximately threefold higher in the screening group than in the control group (6 vs. 2 per 1000 cases per year), while in the United Kingdom Trial of Early Detection of Breast Cancer, the comparable rates were 5.2 versus 1.7 per 1000 cases per year (41). The explanation usually given for this increased incidence in screened versus unscreened populations is that initial screenings detect tumors that would not have been detected until later, producing a transient increase in the screened group. In addition, an overdiagnosis bias may contribute to the increase. During our study period, many women who underwent mammography were doing so for the first time, particularly those 75 years of age and older (15).

The issue of distinguishing screening from diagnostic mammography also challenges all observational studies of mammography that use claims data. Screening mammography is performed on asymptomatic women, while diagnostic mammography (unilateral or bilateral) is performed to investigate an abnormality (for example, a lump felt by a physician or on self-examination). Since diagnostic mammography is ordered to investigate suspicious findings, its yield, or true-positive rate, should be considerably higher than that of screening mammography. Thus, misclassifying diagnostic mammograms as screening mammograms would tend to inflate estimates of sensitivity and positive predictive value. In the context of our study and of previous studies (29, 39, 40), misclassifying a true diagnostic mammogram as a screening mammogram, or vice versa, would also tend to blur the distinction between the screening and nonscreening groups. That is, it would tend to reduce any true difference in tumor size and stage at diagnosis between the women who had previously received screening mammography and those who had not. Missing data on mammography not captured in the claims system (for example, mammography received through free screening programs) would also blur the distinction among screening groups and diminish differences in observed tumor sizes. Greater misclassification of screening groups among women age 69 to 74 years than among women age 75 years and older could produce the patterns seen in **Tables 2** and **3**, where screening mammography was associated with greater reductions in tumor size among women age 75 years and older than in women age 69 to 74 years. However, we can think of no plausible mechanisms that would cause the rate of misclassification to vary substantially by age.

Since our study used the linked SEER–Medicare database, our measures of patient characteristics and screening use are limited to those that can be generated from these data. In particular, since information on each patient's socioeconomic status was not available, we used the median household income in each patient's census tract to measure socioeconomic status (44). This group-level variable estimates the contextual or neighborhood effect of income, which limits our ability to capture individual effects (45).

A major factor contributing to the poor survival of older women with breast cancer is delay in diagnosis (2–6). Our results suggest that the more advanced stage and larger size of breast cancer at diagnosis in older women are not present in women who have at least two screening mammograms in the 2 years before diagnosis. Moreover, we found no evidence that our findings are explained by overdiagnosis or by length or selection biases. Therefore, although our study did not completely assess outcomes such as mortality, survival, and quality of life, our results provide strong, indirect evidence for recommending routine mammography screening in women 75 years of age and older.

Our results do not address the important issue of when to stop mammography. Satariano and Ragland (46) concluded that early diagnosis of breast cancer would confer little or no survival benefit on women with many severe comorbid conditions. A similar argument should hold for very old women. The American Geriatrics Society addressed this issue by suggesting that screening mammography be limited to women with a life expectancy of at least 4 years (24). Further analyses of observational data, which assess survival, may shed more light on how to better define the class of older women likely to benefit from mammography.

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Disclaimer: This study used the linked SEER–Medicare Database. The interpretation and reporting of data from this database are the sole responsibility of the authors.

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ARTICLE

Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections

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Background: Bloodstream infections occurring in persons residing in the community, regardless of whether those persons have been receiving health care in an outpatient facility, have traditionally been categorized as community-acquired infections.

Objective: To develop a new classification scheme for bloodstream infections that distinguishes among community-acquired, health care–associated, and nosocomial infections.

Design: Prospective observational study.

Setting: One academic medical center and two community hospitals.

Patients: All adult patients admitted to the hospital with bloodstream infection.

Measurements: Demographic characteristics, living arrangements before hospitalization, comorbid medical conditions, factors predisposing to bloodstream infection, date of hospitalization, dates and number of positive blood cultures, results of microbiological susceptibility testing, dates of hospital discharge or death, and mortality rates at 3 to 6 months of follow-up.

Results: 504 patients with bloodstream infections were enrolled; 143 (28%) had community-acquired bloodstream infections, 186 (37%) had health care–associated bloodstream infections, and 175 (35%) had nosocomial bloodstream infections. Of the 186 patients with health care–associated bloodstream infection, 29 resided in a nursing home, 64 were receiving home health care, 78 were receiving intravenous or intravascular therapy at home or in a clinic, and 117 had been hospitalized in the 90 days before their bloodstream infection. Cancer was more common in patients with health care–associated or nosocomial bloodstream infection than in patients with community-acquired bloodstream infection. Intravascular devices were the most common source of health care–associated and nosocomial infections, and *Staphylococcus aureus* was the most frequent pathogen in these types of infections. Methicillin-resistant *S. aureus* occurred with similar frequency in the groups with health care–associated infection (52%) and nosocomial infection (61%) but was uncommon in the group with community-acquired bloodstream infection (14%) ($P = 0.001$). Mortality rate at follow-up was greater in patients with health care–associated infection (29% versus 16%; $P = 0.019$) or nosocomial infection (37% versus 16%; $P < 0.001$) than in patients with community-acquired infection.

Conclusions: Health care–associated bloodstream infections are similar to nosocomial infections in terms of frequency of various comorbid conditions, source of infection, pathogens and their susceptibility patterns, and mortality rate at follow-up. A separate category for health care–associated bloodstream infections is justified, and this new category will have obvious implications for choices about empirical therapy and infection-control surveillance.

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A recent review (1) found that nearly equal proportions of bacteremias were community acquired (48%) and nosocomial (52%). In the 1970s, by contrast, nearly two thirds of 500 bacteremic episodes were nosocomial (2). At present, patients with complicated conditions, such as cancer or renal failure, are routinely cared for in outpatient settings, yet such patients are still categorized as having "community-acquired infections" when they are admitted to the hospital with bloodstream infection. The Centers for Disease Control and Prevention (CDC) surveillance definitions include only nosocomial infection (3); infections that are not nosocomial are considered to be community acquired by default.

The term *nosohusial* has been proposed to describe infections occurring in patients who are receiving care at home (4). However, this term applies only to illnesses in patients who receive care at home; it excludes patients in nursing homes and rehabilitation centers, patients receiving dialysis, and patients receiving chemotherapy in physicians' offices. Although the authors of a recent study (5) proposed creating a more inclusive category, health care–associated infection, no consensus definition exists for this group of infections.

We sought to devise a new classification scheme for bloodstream infections that distinguishes among and compares patients with community-acquired, health care–associated, and nosocomial infections.

METHODS

This prospective cohort study was done at Duke University Medical Center (Durham, North Carolina), Durham Regional Hospital (Durham, North Carolina), and Nash General Hospital (Rocky Mount, North Carolina). Approval of the study protocol was obtained from the institutional review boards at each hospital, which waived the requirement for obtaining informed consent.

Patient Selection

Daily microbiology laboratory reports were reviewed and case-report forms were completed by either a physician or an infection-control practitioner on consecutive adult patients who were admitted to the hospital with blood-

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Context

Bloodstream infections are traditionally classified as community-acquired or hospital-acquired (nosocomial). Ideally, these classifications guide initial diagnostic and management decisions. As out-of-hospital care grows more complex, do we need finer classifications?

Contribution

This prospective study from three hospitals in North Carolina shows that about one third of patients with bloodstream infections have had recent contact with the health care system (health care–associated infections) through nursing homes, home health care programs, outpatient intravenous therapy, or recent hospitalizations. *Staphylococcus aureus* and intravascular devices were the most common pathogen and source, respectively, for both health care–associated and nosocomial infections.

Implications

Health care–associated infections often resemble nosocomial infections, a fact to be considered in selecting empirical antibiotic therapy for these infections.

–The Editors

stream infections or developed bloodstream infections during hospitalization. Patients younger than 17 years of age and patients who visited the emergency department but were not hospitalized were excluded.

Data Collection

We collected data on demographic characteristics, medication use, blood cultures, comorbid medical conditions, results of antimicrobial susceptibility testing, and dates of admission and discharge or death. Mortality data were retrieved from medical records and a Social Security death registry Web site (6). The medical record was the gold standard for assessing mortality, and we searched for deaths by Social Security number only if the medical record was not definitive. Follow-up continued for a maximum of 6 months after enrollment.

A *bloodstream-infection episode* was defined by the first set of positive blood cultures in a series or by any new positive blood culture set occurring more than 48 hours after a previous positive result, unless it was clear to the investigator that the new positive culture was part of the previous episode (2). To distinguish between true bloodstream infections and episodes of contamination, each positive blood culture was assessed critically by one investigator. All isolates were categorized as 1) true-positive, 2) contaminated, or 3) of unknown clinical significance. The determination was made after review of the patient's clinical history, physical findings, temperature at the time of blood culture, leukocyte count, number of positive blood cultures, results of cultures of specimens from other sites, imaging results, histopathologic findings, clinical course, and response to therapy (1).

Nosocomial bloodstream infection was defined by a positive blood culture obtained from patients who had been hospitalized for 48 hours or longer (3). If a patient was transferred from another hospital, the duration of inpatient stay was calculated from the date of the first hospital admission.

Health care–associated bloodstream infection was defined by a positive blood culture obtained from a patient at the time of hospital admission or within 48 hours of admission if the patient fulfilled any of the following criteria:

1. Received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before the bloodstream infection. Patients whose only home therapy was oxygen use were excluded.
2. Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before the bloodstream infection.
3. Was hospitalized in an acute care hospital for 2 or more days in the 90 days before the bloodstream infection.
4. Resided in a nursing home or long-term care facility.

Community-acquired bloodstream infection was defined by a positive blood culture obtained at the time of hospital admission or within the 48 hours after hospital admission for patients who did not fit the criteria for a health care–associated infection.

Information about comorbid medical conditions, such as diabetes, chronic obstructive pulmonary disease, liver disease, active cancer, transplantation, or HIV infection, was obtained through medical record review. Active cancer was defined as a solid tumor or hematologic malignancy (except squamous-cell or basal-cell skin cancer) diagnosed or treated in the past 5 years. Vascular disease was defined by the clinical documentation of at least one of the following: coronary artery disease, cerebrovascular disease, peripheral vascular disease, or aortic aneurysm. Renal failure was defined as a serum creatinine concentration greater than 177 μmol/L (>2.00 mg/dL).

Factors predisposing to infection, such as chemotherapy, immunosuppressive therapy, and radiation therapy, were considered to be present if they had been administered within 30 days of the bloodstream infection. Neutropenia was defined as an absolute neutrophil count of less than 500 cells/mm^3 within 30 days before the bloodstream infection. Immunosuppressive therapy included treatment with steroids, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, and calcineurin inhibitors.

Sources of bloodstream infection were designated as culture confirmed (if the same organism was isolated from another site) or suspected (if clinical findings of infection were seen without microbiological proof). *Primary bloodstream infections including intravascular device–associated infections* were defined according to the National Nosocomial Infections Surveillance System (3, 7). *Secondary bloodstream infection* was declared to be present when an organism isolated from a blood culture was related to an infection at another site, as defined by both CDC and other published criteria (3, 8).

Microbiology

All isolates from patients were identified and speciated by using standard microbiologic techniques (2). Antimicrobial susceptibility testing was done according to National Committee for Clinical Laboratory standards (9).

Statistical Analysis

Statistical analysis was done by using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). Distributions of baseline characteristics were analyzed by using the Wilcoxon rank-sum test for continuous variables. The chi-square test was used to assess associations among categorical variables, with 3 × 2 tables broken down into three 2 × 2 tables for pairwise comparisons. If any expected value for a cell in one of the 2 × 2 tables was less than 5, the Fisher exact test was used and two-sided *P* values were reported. Associations between epidemiologic categories of infection and other variables were analyzed by using conditional fixed-effects logistic regression. Dummy variables (0/1) were used to represent two of the three hospitals (the third hospital being the baseline) as well as two of the three epidemiologic categories of infection, thereby adjusting for clustering of epidemiologic factors and outcomes by hospital site. This technique was validated by comparison with Mantel–Haenszel chi-square. A *P* value less than 0.05 was considered statistically significant.

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Between 16 October 2000 and 28 February 2001, a total of 1175 positive blood cultures were detected at the three study hospitals. Of these 1175 cultures, 476 were the result of contamination, 655 represented true bloodstream infections, and 44 were of unknown clinical significance. Seven of the 1175 were excluded from analysis because the patients were not admitted to the hospital.

Coagulase-negative staphylococci (66%), gram-positive rods (16%), and mixed skin flora (9%) constituted most of the contaminants. Either coagulase-negative staphylococci (64%) or yeast (11%) was present in three fourths of cases classified as bloodstream infection of unknown clinical significance.

Five hundred four patients had a total of 648 bloodstream-infection episodes (mean episodes per patient, 1 [range, 1 to 4]). Only the first episode of bloodstream infection was analyzed; subsequent episodes were excluded.

Of the 504 patients, 143 (28%) had community-

Table 1. **Characteristics of 504 Patients with Bloodstream Infections from Three Hospitals***

Characteristic	Patients from DUMC (*n* = 330)	Patients from DRH (*n* = 110)	Patients from NGH (*n* = 64)	Total Patients (*n* = 504)	*P* Values		
					DUMC vs. DRH	DUMC vs. NGH	DRH vs. NGH
Mean age ± SD (median), *y*	58 ± 17 (59)	65 ± 19 (71)	63 ± 20 (67)	60 ± 18 (61)	<0.001	0.069	>0.2
Men, *n (%)*	182 (55)	57 (52)	30 (47)	269 (53)	>0.2	>0.2	>0.2
Race, *n (%)*							
White	194 (59)	67 (61)	18 (28)	279 (55)	>0.2	<0.001	<0.001
Nonwhite	136 (41)	43 (39)	46 (72)	225 (45)			
Living arrangements before hospitalization, *n (%)*							
Private residence	307 (93)	92 (84)	54 (84)	453 (90)	0.16	0.025	>0.2
Other	23 (7)	18 (16)	10 (16)	51 (10)			
Comorbid conditions, *n (%)*							
Vascular disease	130 (39)	49 (45)	26 (41)	205 (41)	>0.2	>0.2	>0.2
Renal failure	113 (34)	20 (18)	21 (33)	154 (31)	0.002	>0.2	0.028
Hemodialysis	46 (14)	5 (5)	10 (16)	61 (12)	0.008	>0.2	0.012
Diabetes mellitus	91 (28)	28 (25)	24 (38)	143 (28)	>0.2	0.11	0.094
Cancer	104 (32)	22 (20)	8 (13)	134 (27)	0.021	0.002	>0.2
Chronic obstructive pulmonary disease	47 (14)	23 (21)	13 (20)	83 (16)	0.098	>0.2	>0.2
Liver disease	32 (10)	1 (1)	6 (9)	39 (8)	0.002	>0.2	0.011
Transplantation	41 (12)	0	0	41 (8)	<0.001	0.003	1.0
HIV infection	15 (5)	5 (5)	5 (8)	25 (5)	1.0	>0.2	>0.2
Factors predisposing to bloodstream infection, *n (%)*							
Immunosuppressive therapy	73 (22)	10 (9)	8 (13)	91 (18)	0.003	0.081	>0.2
Chemotherapy	51 (15)	7 (6)	2 (3)	60 (12)	0.015	0.008	>0.2
Neutropenia	26 (8)	4 (4)	1 (2)	31 (6)	0.13	0.067	>0.2
Radiation therapy	11 (3)	1 (1)	2 (3)	14 (3)	0.18	>0.2	>0.2

* DRH = Durham Regional Hospital; DUMC = Duke University Medical Center; and NGH = Nash General Hospital.

Table 2. **Comorbid Medical Conditions in 504 Patients with Bloodstream Infections, by Epidemiologic Type of Infection***

Condition	Patients with Community-Acquired BSI (*n* = 143)	Patients with Health Care–Associated BSI (*n* = 186)	Patients with Nosocomial BSI (*n* = 175)	*P* Values		
				Community-Acquired BSI vs. Health Care–Associated BSI	Community-Acquired BSI vs. Nosocomial BSI	Health Care–Associated BSI vs. Nosocomial BSI
	←———	*n* (%)	———→			
Renal failure	32 (22)	73 (39)	49 (28)	0.019	>0.2	0.041
Diabetes	39 (27)	57 (31)	47 (27)	>0.2	>0.2	>0.2
Vascular disease	50 (35)	80 (43)	75 (43)	>0.2	0.19	>0.2
Cancer	18 (13)	55 (30)	61 (35)	0.003	0.001	>0.2
Chemotherapy	0 (0)	32 (17)	28 (16)	>0.2	>0.2	>0.2
Neutropenia	0 (0)	13 (7)	18 (10)	>0.2	>0.2	>0.2
Chronic obstructive pulmonary disease	25 (17)	27 (15)	31 (18)	>0.2	>0.2	>0.2
Transplantation	7 (5)	17 (9)	17 (10)	>0.2	>0.2	>0.2
Immunosuppressive therapy	17 (12)	36 (19)	38 (22)	0.17	0.16	>0.2
HIV infection	13 (9)	6 (3)	6 (3)	0.032	0.060	>0.2
Liver disease	8 (6)	20 (11)	11 (6)	>0.2	>0.2	0.096

* BSI = bloodstream infection.

acquired bloodstream infections, 186 (37%) had health care–associated bloodstream infections, and 175 (35%) had nosocomial bloodstream infections. Community-acquired infections occurred more frequently at the two community hospitals (71 of 174 patients [41%]) than at the university teaching hospital (72 of 330 patients [22%]) ($P < 0.001$). Conversely, nosocomial infections occurred more frequently at the university teaching hospital (142 of 330 patients [43%] than at the two community hospitals (33 of 174 patients [19%]) ($P < 0.001$).

First episodes of bloodstream infection comprised 577 isolates from 504 patients; that is, 114 of 504 patients (23%) had polymicrobial infections. Patients had a median of 2 positive blood culture sets (interquartile range [IQR], 1 to 2; range, 1 to 15).

The mean age of the study patients was 60 years. Approximately two thirds of the study cohort was admitted to Duke University Medical Center (**Table 1**). Twenty-nine percent of patients (146 of 504) either were admitted to an intensive care unit after onset of their bloodstream infection or developed a bloodstream infection while in, or within 7 days of being in, an intensive care unit.

Health Care–Associated Bloodstream Infection

Twenty-nine of 186 patients with health care–associated bloodstream infections (16%) resided in a nursing home, 64 (34%) received home health care, 78 (42%) received home- or clinic-based intravenous therapy or dialysis, and 117 (63%) had been hospitalized in the 90 days before their bloodstream infection.

Comorbid Medical Conditions and Factors Predisposing to Bloodstream Infection

The most frequent comorbid medical conditions were vascular disease (41% of the 504 total patients), renal failure (31%), and diabetes mellitus (28%). Diabetes mellitus, vascular disease, and chronic obstructive pulmonary disease were equally common in the three groups of patients (**Table 2**). Renal failure was more common in patients with health care–associated infection; HIV infection was more common in those with community-acquired infection. Cancer was more common in the groups with health care–associated and nosocomial infections than in the group with community-acquired infection (**Table 2**).

Source of Bloodstream Infection

A proven ($n = 234$) or suspected ($n = 210$) source of bloodstream infection was identified in 444 of 504 study patients (88%). Bloodstream infections were considered to be primary in 208 patients (40%) and secondary in 296 patients (60%). An intravascular device was the most common source of bloodstream infection (148 of 444 patients [33%]), and urinary tract infection was the second most common source (114 of 444 patients [26%]).

Patients with health care–associated and nosocomial bloodstream infections had similar frequencies of intravascular-device–related and gastrointestinal tract–related bacteremias, and patients with community-acquired bloodstream infection had more bloodstream infections that were secondary to urinary tract infection (**Table 3**).

Pathogens

The two pathogens most often responsible for community-acquired bloodstream infections were *Escherichia coli* and *Streptococcus pneumoniae*. *Staphylococcus aureus* was the most common pathogen in patients with health care–associated and nosocomial bacteremia. The second and third most common pathogens in patients with nosocomial bloodstream infection were *Staphylococcus epidermidis* and *Enterococcus* species. *Candida* species caused only 2 of 143 community-acquired bloodstream infections, but it caused 10 of 175 nosocomial bloodstream infections ($P = 0.04$).

Microbiological Susceptibility Data

Seventy-three of the 145 patients with bloodstream infection due to *S. aureus* were infected with methicillin-resistant *S. aureus* (MRSA). Only 3 patients with community-acquired bloodstream infection were infected with MRSA (2%); in contrast, 35 of 186 patients (19%) with health care–associated bloodstream infection and 35 of 175 patients (20%) with nosocomial bloodstream infection had MRSA bacteremia. Of the 35 patients with health care–associated cases of MRSA bacteremia, 23 had been hospitalized in the previous 90 days, 15 had received home intravenous therapy or nursing care, 16 were receiving dialysis or chemotherapy, and 8 resided in a nursing home. All 3 patients with community-acquired MRSA infection had been hospitalized in the previous 12 months (one had been hospitalized 6 months before the bacteremia; one, 9 months before the bacteremia; and one, 12 months before the bacteremia).

Enterococci manifesting resistance to ampicillin and vancomycin were more common in patients with nosocomial bloodstream infection than in patients with health care–associated bloodstream infection. They were absent in patients with community-acquired bloodstream infection. Ampicillin–sulbactam and ciprofloxacin resistance occurred with similar frequency in Enterobacteriaciae isolated from patients with health care–associated and those with nosocomial bloodstream infection and was infrequent in the group with community-acquired infection.

Length of Stay and Mortality

The median duration of hospital stay for all study patients was 8.5 days (IQR, 5 to 20 days; range, 0 to 225 days). Patients with nosocomial bloodstream infection had longer median durations of hospital stay (23 days [IQR, 13.5 to 45 days]) than did patients with health care–associated bloodstream infection (7 days [IQR, 4 to 15 days]) or community-acquired bloodstream infection (6 days [IQR, 4 to 8.5 days]).

The crude inpatient mortality rate for all patients with bloodstream infection was 21% (108 of 504 patients). No statistically significant difference was seen in inpatient mortality rates among the three hospitals. However, significantly more in-hospital deaths were seen in the group with nosocomial bloodstream infection (52 of 175 patients [30%]) than in the groups with health care–associated bloodstream infection (37 of 186 patients [20%]; $P = 0.038$) and community-acquired bloodstream infection (19 of 143 patients [13%]; $P = 0.002$). Patients with health care–associated and community-acquired infection did not differ with respect to inpatient mortality rates ($P = 0.15$). A total of 33 patients died 3 to 6 months after hospitalization (of the 504 study patients, a total of 141 died [28%]). The death rate was higher in the group with health care–associated infection than in the group with community-acquired infection (29% versus 16%; $P = 0.019$) and in the nosocomial group than in the community-acquired group (37% versus 16%; $P < 0.001$). The mortality rate at follow-up did not differ in the groups with nosocomial and health care–associated infections ($P = 0.19$).

DISCUSSION

Our definition of health care–associated bloodstream infection was empirically derived after a critical review of several studies published in the past decade. For example, we extended the definition to include patients receiving hemodialysis because they have high rates of bloodstream infection and are often infected or colonized with resistant bacteria as outpatients (10–12). Similarly, residence in a nursing home or other long-term care facility places persons at risk for colonization or infection with MRSA (13–15).

Bloodstream infections that occur in persons who reside in the community have been categorized as community-acquired bacteremias even if the persons are receiving out-of-hospital medical therapy (16, 17). For example, a recent study (18) reported that 91% of 57 episodes of *S. aureus* bacteremia in patients with HIV infection were community acquired, even though 78% of these patients had had an indwelling intravascular catheter when they developed infection. In another study (17), more than one fifth of community-acquired *S. aureus* bacteremias from

Table 3. **Source of Bloodstream Infection, by Epidemiologic Type of Infection***

Source of BSI	Patients with Community-Acquired BSI ($n = 125$)	Patients with Health Care–Associated BSI ($n = 168$)	Patients with Nosocomial BSI ($n = 151$)	*P* Values		
				Community-Acquired BSI vs. Health Care–Associated BSI	Community-Acquired BSI vs. Nosocomial BSI	Health Care–Associated BSI vs. Nosocomial BSI
	←	*n* (%)	→			
Intravascular device	0	70 (42)	78 (52)	NA	NA	>0.2
Urinary tract infection	58 (46)	29 (17)	27 (18)	<0.001	<0.001	>0.2
Pneumonia	34 (27)	27 (16)	24 (16)	0.10	0.18	>0.2
Gastrointestinal tract infection	5 (4)	28 (17)	20 (13)	0.004	0.056	0.15

* BSI = bloodstream infection; NA = not available.

1990 to 1993 were related to intravascular devices; no cases from 1980 to 1983 were related to these devices. Home-based intravenous therapy has an overall incidence of bacteremia of 2% to 4.2% with an estimated risk for bloodstream infection of 2 per 1000 catheter-days (4, 16, 19, 20).

Morin and Hadler (5) recently proposed a definition for a new category, health care–associated bloodstream infections due to *S. aureus*. They categorized community-acquired *S. aureus* bloodstream infections into three groups: "health care–associated," "with underlying medical condition," and "with no underlying medical condition." The category of "health care–associated bloodstream infection" included outpatients with indwelling vascular devices, patients receiving dialysis, and patients who had been hospitalized within the past 12 months. In contrast to us, Morin and Hadler categorized bloodstream infections as nosocomial if patients resided in a nursing home or long-term care facility. Sixty-two percent of patients with community-acquired bacteremia had health care–associated bacteremia, 71% had been hospitalized in the previous 12 months, 32% were receiving hemodialysis, and 49% had an indwelling device.

In results similar to those of Morin and Hadler, we found that 68 of 88 patients who had non-nosocomial bloodstream infections caused by *S. aureus* had health care–associated infections. Sixty-two percent of these 68 patients had been hospitalized in the previous 3 months, 32% were receiving hemodialysis, and 44% had received outpatient intravenous therapy before their bloodstream infection. However, unlike Morin and Hadler, who reported that only 16% of patients with health care–associated *S. aureus* bloodstream infection were infected with MRSA, we found that 51% of our patients with health care–associated bloodstream infections due to *S. aureus* had MRSA infection. This difference in rates of MRSA may reflect differences in the prevalence of MRSA and case-mix between the hospitals in the two studies.

We chose previous hospitalization within 3 months as the criterion by which to categorize patients as having health care–associated bloodstream infection, whereas Morin and Hadler used hospitalization in the preceding 12 months. Had we used Morin and Hadler's criterion, 30 additional patients would have been classified as having had health care–associated bloodstream infections. The 3 patients who were defined as having community-acquired MRSA infection and the 4 patients with resistant gram-negative pathogens would also have been classified as having had health care–associated bloodstream infection. However, all of the remaining 23 patients with community-acquired infection who had been hospitalized within the past year had had bloodstream infections caused by antibiotic-susceptible organisms; 6 were infected with *E. coli*, and 4 were infected with *S. pneumoniae*.

Of 186 patients in our study with health care–associated bloodstream infection, 117 (63%) had been hospitalized in the preceding 3 months. Previous hospitalization is a known risk factor for colonization with MRSA, vancomycin-resistant enterococci, and fluoroquinolone-resistant gram-negative organisms in patients residing both in the community and in long-term care facilities (14, 21, 22), and asymptomatic colonization with both MRSA and vancomycin-resistant enterococci may persist for months to years (23–25).

Patients with health care–associated bloodstream infections in our cohort closely resemble those with nosocomial infections in the following ways: 1) frequency of cancer and HIV infection, 2) source of infection, 3) frequency of *S. aureus* and MRSA as pathogens, and 4) mortality rates at follow-up. Notable differences between the two groups were seen in frequency of renal failure, duration of hospital stay, and inpatient mortality rate.

Nosocomial bloodstream infections are often caused by *S. epidermidis*, are associated with the use of intravascular catheters, and result in both increased length of stay and increased crude mortality rates (26, 27). In our study, *S. epidermidis* caused 44 of 175 nosocomial bloodstream infections (25%); intravascular catheters were the source of infection in 78 of 175 patients (45%). Length of stay and in-hospital mortality rate were greater in the group with nosocomial bloodstream infection than in other groups.

This study has limitations. Our results may have been biased by local patterns of health care and antimicrobial resistance that are different from those in other areas of the world. Given the large populations served by the three study hospitals, their overlap with areas served by other hospitals, and the many agencies providing community-based health care in the region, we could estimate neither a suitable denominator nor the actual incidence of bloodstream infection by each individual category.

Finally, our definition of health care–associated bloodstream infection may have been excessively broad in some aspects, yet imprecise in other ways. For example, the 3-month cut-off for recent hospitalization could have been expanded to 12 months in light of the long-lived persistence of colonization with resistant bacteria (23–25). In addition, our category of health care–associated infections includes a heterogeneous group of persons, and not all subsets of this group are identical in their risks for and predictors of infection.

Our results suggest that empirical antibiotic therapy for patients with known or suspected health care–associated and nosocomial bloodstream infections should be similar. In contrast, patients with community-acquired bloodstream infection are often infected with antibiotic-sensitive organisms, and their prescribed therapy should reflect this pattern.

For the reasons cited above, a category for health care–associated bloodstream infection is needed. Future studies should validate this category for infections other than bloodstream infections and examine subsets of patients with health care–associated infections. The CDC and individual hospital infection-control surveillance programs should redefine infections to accommodate a new category of health care–associated infections. Collecting surveillance data on health care–associated and nosocomial infections would help clinicians choose empirical antibiotic therapy and would have obvious implications for professionals involved in the care of sick patients in community settings.

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Use of Postmenopausal Hormones, Alcohol, and Risk for Invasive Breast Cancer

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Background: **Physiologic evidence suggests that use of alcohol increases the risk for breast cancer through a hormonal mechanism, but the relationship among breast cancer, alcohol, and postmenopausal hormones (PMH) remains unclear.**

Objective: **To examine the relation between concurrent use of alcohol and PMH and invasive breast cancer.**

Design: **Prospective cohort study**

Setting: **Nurses' Health Study.**

Participants: **44 187 postmenopausal women.**

Measurements: **Self-reported data on PMH use and breast cancer obtained from biennial questionnaires completed from 1980 to 1994 and average alcohol consumption in 1980, 1984, 1986, and 1990.**

Results: **1722 women developed invasive breast cancer. Risk for breast cancer was elevated in women who currently used PMH for 5 or more years and did not drink alcohol (relative risk, 1.32 [95% CI, 1.05 to 1.66]) and those who never used PMH but drank 20 or more g (1.5 to 2 drinks) of alcohol daily (relative risk, 1.28 [CI, 0.97 to 1.69]). Current users of PMH for 5 or more years who consumed 20 or more g of alcohol daily had a relative risk for breast cancer nearly twice (1.99 [CI, 1.42 to 2.79]) that of nondrinking nonusers of PMH. A hypothetical postmenopausal woman whose lifetime risk for breast cancer is 4% could increase her risk to 8% with 5 or more years of current PMH use and consumption of more than one alcoholic drink daily.**

Conclusions: **Both alcohol consumption and PMH use were associated with an increased incidence of breast cancer. Women who are currently taking PMH may want to consider the added risks of regular alcohol consumption.**

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Since the first epidemiologic study linking risk for breast cancer and alcohol consumption (1), many mechanisms have been postulated to explain how alcohol intake increases the risk for breast cancer. These proposed mechanisms include disruption of cell membrane integrity, direct cytotoxic effect, interference with DNA repair, and impairment of hepatic metabolism of carcinogens. Physiologic evidence strongly suggests that alcohol increases risk for breast cancer, at least in part, by altering circulating steroid hormone levels. In premenopausal women, alcohol consumption increased both plasma and urinary levels of estradiol and estrone by 15% to 30%, depending on the phase of the menstrual cycle (2). In postmenopausal women taking postmenopausal hormones (PMH), acute ingestion of alcohol caused an average increase of 300% in estradiol levels compared with placebo. This effect of alcohol was not demonstrated in women not taking PMH (3). Although both PMH use and alcohol consumption are important modifiable risk factors in the development of invasive breast cancer in postmenopausal women, the interaction between the two has not been well quantified.

The magnitude of the risk for breast cancer associated with PMH use has been clarified as follow-up has accumulated in large prospective cohort studies. In a reanalysis of worldwide data, a relative risk for breast cancer of 1.35 (95% CI, 1.21 to 1.49) was reported among current users of PMH for 5 or more years compared with never-users (4).

Alcohol intake has also been consistently associated with an increased risk for breast cancer. In a pooled analysis of six large prospective cohort studies, multivariable relative risks were 1.16 (CI, 0.98 to 1.38) for women who consumed 15.0 to 30.0 g of alcohol daily (about 1.5 to 2.5 drinks) and 1.41 (CI, 1.18 to 1.69) for those who consumed 30.0 to 60.0 g/d (about 2.5 to 4 drinks) compared with women who did not drink alcohol (5). A meta-analysis that used data from both cohort and case–control studies had similar findings (6).

Previous epidemiologic studies have been inconclusive in characterizing the interaction between alcohol and PMH use. With shorter follow-up in the Nurses' Health Study, exploratory analyses revealed that risk for breast cancer was elevated in users of PMH who drank more than 15 g of alcohol daily (age-adjusted relative risk, 1.56 [CI, 1.2 to 2.0]) but not in PMH users who did not drink alcohol (age-adjusted relative risk, 0.99 [CI, 0.62 to 1.60]). At that time, the confidence intervals were wide and there was insufficient power to further characterize the interaction (7). The Iowa Women's Health Study, a prospective cohort study of 41 837 postmenopausal women, reported similar results after 3 years of follow-up. When alcohol abstainers and never-users of PMH were used as the reference group, PMH users who did not drink alcohol had a multivariable relative risk for breast cancer of 0.88 (CI, 0.67 to 1.15) compared with 1.83 (CI, 1.18 to 2.85) for PMH users who consumed more than 15 g of alcohol daily (8). Several case–control studies, however, found no difference in the alcohol effect between PMH users and nonusers (9–13). The recent pooled analysis did not find an interaction between PMH and alcohol consumption, but the failure to update information on alcohol and PMH use may have led to misclassification of concurrent use (5).

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Therefore, we sought to clarify the risks of alcohol and PMH use, both separately and concurrently.

METHODS

The Nurses' Health Study cohort was established in 1976, when 121 700 female registered nurses 30 to 55 years of age completed a baseline questionnaire that included items on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been mailed to update information.

Dietary Data

Dietary information was first collected in 1980, when participants completed a semi-quantitative food-frequency questionnaire and reported their average frequency of consumption of specific food and beverage items during the previous 12 months. Consumption of beer, wine, and spirits was ascertained in separate items. Alcohol consumption, in grams per day, was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g of alcohol per 12-oz serving of beer, 11.0 g per 4-oz serving of wine, and 14.0 g per standard serving of spirits) (14). The dietary data were updated in 1984, 1986, and 1990. Alcohol intake as measured by the food-frequency questionnaire was highly correlated with intake as calculated from detailed food diaries completed by a sample of study participants (Spearman rank-correlation coefficient = 0.90) (15).

Sample for Analysis

In 1980, 98 462 nurses returned the dietary questionnaires. Women who left 10 or more food items blank (4%), those with implausibly high or low scores for total food intake (2.7%), and those who reported any diagnosis of cancer (except nonmelanoma skin cancer) before 1980 were excluded from analysis. Women who developed any type of cancer (except nonmelanoma skin cancer) were censored at the time of their report of the diagnosis.

Our analysis is limited to postmenopausal women. A woman was classified as postmenopausal from the time she returned a questionnaire reporting natural menopause or hysterectomy with bilateral oophorectomy. Self-report of natural menopause and extent of ovarian surgery has been shown to be highly accurate and reproducible (16). Women who reported that their menses ended after hysterectomy without bilateral oophorectomy were considered hormonally premenopausal and were thus excluded from the analysis until the age at which natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers), at which time they were considered postmenopausal. Menopausal status was updated every 2 years, and the sample was expanded to include women who became postmenopausal after 1980. Women for whom information on a covariate or exposure, such as use of PMH or alcohol, was missing on a specific questionnaire were excluded from the analysis for that 2-year period but reentered the analysis when the information was complete. The **Appendix Table** (available at www.annals.org) shows the distribution of missing data.

Context

Evidence links alcohol and breast cancer and suggests a hormonal mechanism. However, the relationships between alcohol, postmenopausal hormone use, and breast cancer are unclear.

Contribution

Using self-reported data from a cohort of nurses, this study showed that ≥1.5 drinks/d and ≥5 years of postmenopausal hormone replacement therapy are associated with increased risk for breast cancer. The relative risk for breast cancer was 1.32 for postmenopausal hormones alone, 1.28 for alcohol alone, and 1.99 for both.

Implications

Women should consider increased risk for breast cancer when deciding about drinking alcohol, taking postmenopausal hormones, and, especially, both together.

–The Editors

For this analysis, 27 262 women met the aforementioned criteria and entered the initial follow-up period (1980 to 1982). By 1994, the beginning of the final 2-year follow-up period, 44 186 women were postmenopausal and eligible for analysis.

Identification of Cases of Breast Cancer

The primary end point was diagnosis of invasive breast cancer. On each questionnaire, we asked whether breast cancer had been diagnosed and, if so, the date of diagnosis. We routinely searched the National Death Index for deaths among women who did not respond to the questionnaires. We asked all women who reported breast cancer (or next of kin for those who had died) for permission to review the pertinent medical records for confirmation. Pathology reports, obtained in 96% of cases, showed a 99.4% confirmation rate. Because of the accuracy of participants' self-reports, analyses were based on all cases of incident invasive breast cancer. Carcinomas in situ were excluded. Follow-up of the cohort for identification of nonfatal breast cancer was 95% complete.

Statistical Analysis

Follow-up began in 1980 and terminated with the diagnosis of any type of cancer, death, or 1 June 1996, whichever came first. Use of PMH (current, past, or never) at the time of the questionnaire was used to define the subsequent 2-year period. Alcohol intake for the first follow-up period was defined by the response to the 1980 dietary questionnaire and was updated with responses from the 1984, 1986, and 1990 questionnaires. For the 2-year periods in which dietary questionnaires were not readministered, alcohol intake from the previous period was used.

Table 1. **Alcohol Consumption, Postmenopausal Hormone Use, and Risk Factors for Breast Cancer among Postmenopausal Women in the Nurses' Health Study in 1982 and 1994***

Characteristic	Year	
	1982	1994
Participants, *n*	29 867	44 186
Median age, *y*	55.8	62.7
Alcohol intake		
Mean, *g/d*	6.8	5.3
Median, *g/d*	1.8	1.1
Average daily intake, *n (%)*		
None	9842 (33.0)	17 439 (39.5)
0.1–4.9 g	9419 (31.5)	14 333 (32.4)
5.0–9.9 g	3102 (10.4)	4389 (9.9)
10.0–19.9 g	4708 (15.8)	51[illegible] (11.6)
≥20.0 g	2796 (9.4)	2914 (6.6)
Type of menopause, *n (%)*		
Natural	19 583 (65.6)	27 202 (61.6)
Surgical†	7203 (24.1)	7812 (17.7)
Other	3081 (10.3)	9172 (20.8)
Postmenopausal hormone use, *n (%)*		
Never	16 150 (54.1)	14 189 (32.1)
Past	7567 (25.3)	9889 (22.4)
Current, <5 years' duration	2649 (8.9)	6119 (13.8)
Current, ≥5 years' duration	3501 (11.7)	13 989 (31.7)
Type of PMH use		
Estrogen alone	5791 (94.2)	11 164 (55.5)
Estrogen and progesterone	194 (3.2)	8222 (40.9)
Other	165 (2.7)	722 (3.6)

* Not all percentages may total 100% because of rounding errors. PMH = postmenopausal hormones.

† Defined as both hysterectomy and bilateral oophorectomy.

Despite the high correlation between alcohol consumption in 1980 and 1990 (Spearman rank-correlation coefficient = 0.71; $P < 0.001$), updated alcohol intake was chosen because analyses that used 1980 alcohol consumption without updating failed to show as consistent a dose–response relationship.

Postmenopausal women were categorized into 1 of 20 groups according to average daily alcohol intake (no alcohol, <2 drinks/wk [0.1 to 4.9 g/d], 3 to 6 drinks/wk [5.0 to 9.9 g/d], about 1 drink/d [10.0 to 19.9 g/d], or ≥2 drinks/d [≥20.0 g/d]) and PMH use (never, past, current with <5 years' use, or current with ≥5 years' use). The alcohol use categories divided the cohort into 5 groups of roughly equivalent size. Current PMH users were classified into those who used PMH for less than 5 years or 5 or more years because the effect of PMH on risk for breast cancer is significantly greater with longer duration of use (4).

Relative risks were calculated as a measure of association. Pooled logistic regression, which approximates the results of time-dependent proportional hazards models when intervals between outcome events are short and the probability of an event in each interval is small (17), was used to compute age-adjusted and multivariable-adjusted relative risks and 95% CIs. Covariates in the model included age (continuous), age at menopause (continuous), type of menopause (natural, surgical with bilateral oophorectomy, other), age at menarche (continuous), parity (nulliparous, 1 to 2 births, >2 births), age at first birth (nulliparous, <22 years, 23 to 25 years, >25 years), weight gain of more than 10 kg since 18 years of age (yes or no), family history of breast cancer in a first-degree relative (yes or no), and self-report of benign breast disease (yes or no). An interaction between alcohol and PMH use was evaluated by using a likelihood ratio test with a cross-product interaction term representing the duration of PMH use and alcohol intake and a Wald test comparing the parameter estimates for alcohol effect among different categories of PMH use. For all covariates, complete case analysis was performed. All analyses were performed by using SAS software, version 6.0 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The research was completely funded by the National Institutes of Health. The funding source had no part in collecting, analyzing, or interpreting the data.

RESULTS

During 557 984 person-years of follow-up, 1722 cases of invasive breast cancer were identified among postmenopausal women with complete data on alcohol and PMH use. **Table 1** shows the distribution and changes over time in alcohol and PMH use. Questions about specific types of PMH were first asked in 1982. Consistent with national trends (18, 19), alcohol use has decreased and PMH use has increased. In 1982, 11.7% of the postmenopausal cohort were current PMH users, which more than doubled to 31.7% in 1994. Among PMH users, estrogen alone remained the most popular therapy, but combination estrogen and progesterone gained popularity, increasing from 3.2% to 40.9% of current PMH users in 1994.

Table 2 shows the main effect of alcohol and PMH use. Risk for breast cancer increased with both increasing alcohol intake and PMH use. Current PMH use was more strongly associated with risk for breast cancer than was past use, and current use for 5 or more years was associated with greater risk than was less than 5 years of use. Consumption of 10.0 to 19.9 g of alcohol daily was associated with a multivariable relative risk of 1.22 (CI, 1.06 to 1.42), and consumption of 20.0 or more g of alcohol daily was associated with a multivariable relative risk of 1.33 (CI, 1.12 to 1.58), consistent with a linear relationship. At consumption of less than 10.0 g of alcohol daily, risk for breast cancer was not significantly increased (relative risk, 1.07 [CI, 0.95 to 1.20]) for 0.1 to 4.9 g/d and 0.99 [CI, 0.83 to 1.18] for 5.0 to 9.9 g/d). The test for trend for alcohol (analyzed as a continuous variable) was significant ($P < 0.001$).

To investigate the effect of concurrent alcohol and PMH use, postmenopausal women were classified into 1 of 20 categories according to alcohol and PMH use (**Table 3**). Compared with nondrinkers who never used PMH, current PMH users for 5 or more years who consumed 20 or more g of alcohol daily had an adjusted relative risk for

Table 2. **Relative Risk for Invasive Breast Cancer in Postmenopausal Women, by Alcohol Intake and Postmenopausal Hormone Use, 1980–1996**

Substance	Cases of Breast Cancer, *n*	Person-Years	Age-Adjusted Relative Risk	Multivariable Relative Risk*
Alcohol intake†				
None	594	205 686	1.00 (referent)	1.00 (referent)
0.1–4.9 g/d	538	177 176	1.08 (0.96–1.22)	1.07 (0.95–1.20)
5.0–9.9 g/d	166	57 346	1.01 (0.85–1.20)	0.99 (0.83–1.18)
10–19.9 g/d	257	73 194	1.24 (1.07–1.44)	1.22 (1.06–1.42)
≥20.0 g/d	167	44 582	1.34 (1.13–1.58)	1.33 (1.12–1.58)
Postmenopausal hormone use				
Never	680	243 286	1.00 (referent)	1.00 (referent)
Past	378	130 554	0.96 (0.84–1.09)	1.05 (0.92–1.20)
Current, <5 years	262	75 874	1.39 (1.20–1.60)	1.37 (1.18–1.59)
Current, ≥5 years	402	108 270	1.27 (1.12–1.44)	1.49 (1.29–1.74)

* Adjusted for age at menarche, age at menopause, age, age at first birth, parity, type of menopause, family history of breast cancer, benign breast disease, postmenopausal hormone use, and weight gain ≥10 kg since 18 years of age.

† Alcohol consumption was updated in 1980, 1984, 1986, and 1990. Alcohol content per drink was 12.8 g of alcohol per serving of beer, 11.0 g of alcohol per serving of wine, and 14.0 g of alcohol per serving of liquor.

breast cancer of 1.99 (CI, 1.41 to 2.79). In contrast, the adjusted relative risk was 1.32 (CI, 1.05 to 1.66) in women taking PMH for 5 or more years who consumed no alcohol and 1.28 (CI, 0.97 to 1.69) in never-users of PMH who consumed 20 or more g of alcohol daily.

As seen with the main effect of alcohol, average alcohol intake of less than 10 g/d did not significantly increase the risk for breast cancer in women who did not take PMH, compared with those who did not take PMH and consumed no alcohol. Similarly, for current PMH users who drank less than 10 g of alcohol daily, the risk was not increased above that for current PMH users who did not drink alcohol. Therefore, intake of less than 10 g of alcohol daily does not modify the relation between PMH and breast cancer risk, since the strength of the association with PMH was consistent in alcohol abstainers and light drinkers. The converse was true as well: The lack of a strong association for light drinkers was consistent in both PMH users and nonusers.

Alcohol consumption of 10 or more g/d was significantly associated with increased risk for breast cancer in both PMH users and nonusers. With use of the relative risk estimates, the interaction between alcohol and PMH appears to be slightly greater than a multiplicative model:

Table 3. **Relative Risk for Invasive Breast Cancer in Postmenopausal Women, by Concurrent Postmenopausal Hormone and Alcohol Use, 1980–1996**

Alcohol Intake, *g/d*	Postmenopausal Hormone Use	Cases of Breast Cancer, *n*	Person-Years	Multivariable Relative Risk (*n* = 1722)*
None	Never	250	46 377	1.00 (referent)
	Past	134	24 613	1.04 (0.84–1.29)
	Current, <5 years	88	12 500	1.45 (1.13–1.86)
	Current, ≥5 years	122	19 353	1.31 (1.05–1.66)
0.1–4.9	Never	201	37 946	1.00 (0.83–1.20)
	Past	84	12 873	1.18 (0.95–1.48)
	Current, <5 years	131	17 569	1.38 (1.07–1.78)
	Current, ≥5 years	131	17 569	1.59 (1.27–1.98)
5.0–9.9	Never	62	11 986	1.00 (0.75–1.32)
	Past	33	6496	0.99 (0.69–1.43)
	Current, <5 years	27	4427	1.27 (0.85–1.89)
	Current, ≥5 years	44	5766	1.61 (1.16–2.24)
10.0–19.9	Never	102	15 500	1.27 (1.01–1.60)
	Past	56	8666	1.26 (0.94–1.69)
	Current, <5 years	34	5204	1.35 (0.94–1.94)
	Current, ≥5 years	65	7227	1.90 (1.44–2.52)
≥20.0	Never	65	9834	1.28 (0.97–1.69)
	Past	33	5304	1.22 (0.85–1.77)
	Current, <5 years	29	2933	2.08 (1.41–3.08)
	Current, ≥5 years	40	4220	1.99 (1.41–2.79)

* Adjusted for age at menarche, age at menopause, age, age at first birth, parity, type of menopause, family history of breast cancer, benign breast disease, and weight gain ≥ 10 kg since 18 years of age.

1.28 (nondrinking PMH users) × 1.32 (never–PMH users who drank ≥20 g/d) = 1.69, which is less than the observed relative risk of 1.99 (PMH users who drank ≥20 g/d). However, no significant statistical interaction or effect modification was observed between PMH use and alcohol intake of more than 20 g/d. In other words, there was no greater risk associated with using both PMH and alcohol together than would be expected from using either one alone.

We also analyzed the alcohol and PMH categories stratified by the presence or absence of a weight change of more than 10 kg since 18 years of age. To increase power to detect differences, alcohol consumption was divided into three categories corresponding to 10-g/d differences in intake. The effect of alcohol and PMH tended to be stronger in women who had gained less than 10 kg since 18 years of age (data not shown), but an interaction term was not significant. Stratified analyses by folate intake and alcohol and PMH categories resulted in small case numbers and less stable risk estimates.

To avoid misclassification of menopausal status, only person-time for women who were known to be postmenopausal or had surpassed the age when more than 90% of the cohort was menopausal was included. The PMH effect may differ in premenopausal or perimenopausal women, who have higher endogenous estrogen levels than do postmenopausal women. The relative risks did not change substantially when analyses were restricted to women who had bilateral oophorectomy or natural menopause (20, 21). Cigarette smoking was considered as a potential confounder, but the associations did not change significantly with the addition or exclusion of smoking in the model. Analyses excluding and including carcinomas in situ yielded similar results (**Appendix Table**, available at www.annals.org). Since not all invasive breast cancers evolve from carcinomas in situ, nor do all carcinomas in situ progress to invasive breast cancer, only analyses limited to invasive breast cancer were reported.

Despite the recent increase in estrogen and progesterone use, combination therapy represents less than 10% of the total person-time of current PMH users. Alcohol categories had to be collapsed for this analysis. Among women who consumed less than 10 g of alcohol per day, a trend was observed toward increased risk in current users of combination PMH therapy for less than 5 years (relative risk, 1.23 [CI, 1.03 to 1.46] for estrogen alone and 1.63 [CI, 1.31 to 2.03] for combination therapy) and 5 or more years (relative risk, 1.63 [CI, 1.31 to 2.03] for estrogen alone and 1.69 [CI, 1.34 to 2.13] for combination therapy). For women who consumed 10 or more g of alcohol daily, no significant difference was observed between current users for less than 5 years (relative risk, 1.60 [CI, 1.12 to 2.29] for estrogen alone and 1.37 [CI, 0.92 to 2.06] for combination therapy) and current users for 5 or more years (relative risk, 1.76 [CI, 1.37 to 2.27] for estrogen alone and 1.34 [CI, 0.87 to 2.07] for combination therapy). Since the confidence intervals overlap and there were relatively few regular alcohol consumers who used combination therapy, no conclusions can be drawn as to whether a true difference exists. Average duration of unopposed estrogen use was longer than that of combination therapy.

DISCUSSION

In this analysis of long-term follow-up in the Nurses' Health Study, alcohol and PMH use were independent risk factors for development of invasive breast cancer. Current users of PMH for 5 or more years who also consumed 20 or more g of alcohol (1.5 to 2 drinks) daily had almost twice the risk for breast cancer (multivariable relative risk, 1.99 [CI, 1.41 to 2.79]) as those who did not drink alcohol and never used PMH. Our results imply that a hypothetical postmenopausal woman with a lifetime risk for breast cancer of 4% in the absence of alcohol or PMH use would increase her risk to 6% (relative risk, 1.49) with current PMH use for at least 5 years and to 8% (relative risk, 1.99) with the concurrent consumption of more than 1 drink/d. We could not detect a large difference between women who drink alcohol less regularly (<10 g or 1 drink/d) and those who do not drink alcohol.

Our current study provides greater power to examine an interaction effect, with longer follow-up and more than three times as many cases as the Iowa Women's Health study. We separately analyzed past and current PMH users. The effects of PMH can appear weaker when past and current users are combined, since risk for breast cancer is most closely tied to current use and returns to baseline with past use (4, 22). For alcohol, the same seems to hold true. In the meta-analysis of alcohol and breast cancer, the studies with the longest duration since assessment of alcohol intake were those that showed the weakest effect, suggesting that recent exposure is more important than past exposure (6). Similarly, our analyses using baseline 1980 alcohol consumption without updating information failed to show as consistent a dose–response relationship. In addition, the synergy of alcohol and PMH with blood estrogen levels appears to reflect an acute effect (3). Because the pooled analysis of cohort studies of alcohol and breast cancer did not update PMH and alcohol use, the interaction between concurrent PMH therapy and alcohol use was not examined in as much detail as in the current study (5). Previous studies that did not find an effect of PMH on development of breast cancer may not have adequately controlled for alcohol use, which may be less prevalent among "healthy" PMH users; this effect would lead to an apparently lower risk for breast cancer compared with non-PMH users who may consume more alcohol.

The effect of average consumption of more than three alcoholic drinks daily could not be adequately evaluated within our cohort, since only a small proportion of participants consumed that much alcohol. However, the drinking habits of our sample were fairly representative of U.S.

women of the same age group (18, 19, 23). Because regularity of drinking was not assessed, we cannot determine whether binge drinking and daily moderate drinking that provides the same average alcohol intake would have similar effects.

Because this was an observational study and PMH and alcohol use was not randomly assigned, other unobserved factors may explain differences in risk for breast cancer. However, the consistency of the results by duration of hormone use and amount of alcohol and the stability of the results, regardless of whether other risk factors for breast cancer were considered, make a true relationship more likely. For an unobserved confounder with a prevalence of 10% to explain a relative risk of 2.0, the association between that unobserved variable and breast cancer would need to be greater than 4.0 (allowing the association between the confounder and alcohol and PMH use to vary from 1.5 to 10.0) (24). Misclassification of women with simple hysterectomy would tend toward underestimation of the risk of PMH use (20, 21).

Sensitivity analyses were performed to evaluate the effect of missing data. In all scenarios, relative risks changed by less than 10%. Although complete case analysis provides the most valid estimates when data are missing completely at random (a very stringent assumption), the prevalence of missing data in our cohort was generally low and therefore unlikely to introduce substantial bias, regardless of the mechanism of the missing data. Observational studies also depend on self-reported data. Since alcohol use was measured accurately in our cohort, correction for measurement error results in relative risks that are only minimally weakened (25, 26). Observational data may remain our main source of information, since a long-term randomized trial of alcohol and PMH use will probably never be performed.

In summary, women who are currently taking or contemplating starting PMH therapy should consider the effects of concurrent alcohol consumption on their risk for breast cancer. We could not show evidence for a statistical interaction between alcohol and PMH. However, the lack of a significant statistical interaction does not support or refute the hypothesis that alcohol mediates risk for breast cancer through hormone levels. Instead, the lack of a statistical interaction implies that the absolute excess risks associated with alcohol exist across all levels of PMH use. Our study suggests that women taking PMH who consume an average of more than one alcoholic drink daily have a significantly increased risk for breast cancer, independent of the risk associated with PMH alone. Longer follow-up is required to evaluate whether combination estrogen and progesterone therapy interacts differently with alcohol than does unopposed estrogen. In addition, the deleterious effects of alcohol on the development of breast cancer need to be weighed against the beneficial effects of light to moderate alcohol drinking on cardiovascular disease and overall mortality (27, 28).

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He is dead, and I feel an odd triumph about it. He is dead, the thing (when I was small) I used to dread more than any other, but I'm still here, my mother's still here, I can hear her breathing, the world has ended but we've survived, we're OK.

He is dead—no rage against the dying of the light, no terror and delirium, only a nightlight smothered in its own wax. Sitting here, the body silent between us as we peer into it for a sign of some kind, I'm on a shock-induced high. If I listen hard enough, I know I'll hear his own count-your-blessings verdict: "Well, that wasn't so bad, was it? When I think how it could have been—drawn-out, or abrupt and messy, or in hospital rather than here—it makes me feel lucky. A good death and a good life too: who could beat it?"

Blake Morrison
And When Did You Last See Your Father?
New York: Picador; 1996:149

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

COMPLEMENTARY AND ALTERNATIVE MEDICINE SERIES
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ACADEMIA AND CLINIC

Complementary and Alternative Medicine for Menopausal Symptoms: A Review of Randomized, Controlled Trials

Fredi Kronenberg, PhD, and Adriane Fugh-Berman, MD

Background: **Women commonly use soy products, herbs, and other complementary and alternative medicine (CAM) therapies for menopausal symptoms. Randomized, controlled trials have evaluated the efficacy and short-term safety of these therapies.**

Purpose: **To review randomized, controlled trials of CAM therapies for menopausal symptoms in order to better inform practice and guide future research.**

Data Sources: **Searches of MEDLINE for articles published from January 1966 through March 2002, of the Alternative and Complementary Database (AMED) of the British Library for articles published from January 1985 through December 2000, and of the authors' own extensive files. Search terms were *hot flash/flush, menopause,* and *climacteric,* combined with *phytoestrogens, alternative medicine, herbal medicine, traditional medicine, Traditional Chinese Medicine (TCM), Ayurveda, naturopathy, chiropractic, osteopathy, massage, yoga, relaxation therapy, homeopathy, aromatherapy,* and *therapeutic touch.***

Study Selection: **29 randomized, controlled clinical trials of CAM therapies for hot flashes and other menopausal symptoms were identified; of these, 12 dealt with soy or soy extracts, 10 with herbs, and 7 with other CAM therapies.**

Data Extraction: **Each author extracted information from half of the studies on the number of patients, study design, outcome measures, and results; the other author then checked these results.**

Data Synthesis: **Soy seems to have modest benefit for hot flashes, but studies are not conclusive. Isoflavone preparations seem to be less effective than soy foods. Black cohosh may be effective for menopausal symptoms, especially hot flashes, but the lack of adequate long-term safety data (mainly on estrogenic stimulation of the breast or endometrium) precludes recommending long-term use. Single clinical trials have found that dong quai, evening primrose oil, a Chinese herb mixture, vitamin E, and acupuncture do not affect hot flashes; two trials have shown that red clover has no benefit for treating hot flashes.**

Conclusions: **Black cohosh and foods that contain phytoestrogens show promise for the treatment of menopausal symptoms. Clinical trials do not support the use of other herbs or CAM therapies. Long-term safety data on individual isoflavones or isoflavone concentrates are not available.**

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Women are frequent users of complementary and alternative medicine (CAM) therapies in many countries (1–5), including the United States, where women use CAM therapies more often than men (48.9% vs. 37.8%) (6). Many women report using these therapies for menopausal symptoms (7, 8). A national magazine received more than 15 000 responses to a survey of alternative treatments for menopausal women (7). Primary symptoms included hot flashes, joint pain, sleep problems, forgetfulness, and fatigue; hot flashes (the most common menopausal symptom for women in the United States) (9) were most commonly treated. Therapies of choice were herbal remedies, chiropractic, and meditation. Recently, dietary supplements and foods containing phytoestrogens have become increasingly popular, despite the lack of data from clinical trials.

The science of CAM therapies is still inadequate to sufficiently inform clinicians and the public of the benefits or potential risks of CAM therapies. To provide information for clinicians, we reviewed randomized, controlled clinical trials of CAM therapies for menopausal symptoms.

METHODS

Study Selection

We searched MEDLINE from January 1966 to December 2002, the Alternative and Complementary Database (AMED) of the British Library from January 1985 to December 2000, and our own extensive files. Databases were searched under the terms *hot flash/flush, menopause,* and *climacteric,* combined with *phytoestrogens, alternative medicine, herbal medicine, traditional medicine, Traditional Chinese Medicine (TCM), Ayurveda, naturopathy, chiropractic, osteopathy, massage, yoga, relaxation therapy, homeopathy, aromatherapy,* and *therapeutic touch.* We did not limit the search to English-language literature. Studies that examined single symptoms or conditions that are not clearly associated with menopause (for example, anxiety and lipids) were excluded. All other randomized, controlled trials, regardless of their quality, were included. A total of 29 studies were identified. Each author extracted information on the number of patients, study design, outcome measures, and results for half the studies; the other author then checked results.

Role of the Funding Source

The funding source had no role in the design, conduct, analyses, or reporting of the study or the decision to submit the manuscript for publication.

CAM THERAPIES

Herbal Remedies

Herbs used in the United States for menopausal problems include black cohosh (*Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*),

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Table 1. **Herbs for Menopausal Symptoms***

Study, Year (Reference)	Country	Design	Patient Characteristics and Age
Black cohosh			
Jacobson et al., 2001 (10)	United States	Randomized, double-blind, placebo-controlled trial	85 women (68 completed the study) with breast cancer and daily hot flashes; 59 women were using tamoxifen concurrently Age, >18 y
Warnecke, 1985 (11)	Germany	Randomized, open, treatment-controlled trial	60 women (48 menopausal; 55 completed study) with menopausal symptoms Age, 45–60 y
Stoll, 1987 (12)	Germany	Randomized, double-blind, placebo-controlled trial	80 women (41 menopausal; 75 completed the study) with climacteric symptoms, >3 hot flashes daily, and "psychic complaints" Age, 46–58 y
Lehmann-Willenbrock and Riedel, 1988 (13)	Germany	Randomized, treatment-controlled trial	60 women (41 menopausal) with climacteric symptoms who had had hysterectomy and had at least 1 ovary Age, ≥40 y
Red clover			
Baber et al., 1999 (14)	Australia	Randomized, double-blind, placebo-controlled crossover trial	51 postmenopausal women (43 completed the study) with >3 hot flashes daily Age, 45–65 y
Knight et al., 1999 (15)	Australia	Randomized, double-blind, placebo-controlled trial	37 postmenopausal women (34 completed the study) with >3 hot flashes daily Age, 40–65
Dong quai			
Hirata et al., 1997 (16)	United States	Randomized, double-blind, placebo-controlled trial	71 postmenopausal women (61 completed the study) with >14 hot flashes weekly (any severity) or >5 hot flashes weekly (moderate or severe) Age, 45–69 y
Evening primrose oil			
Chenoy et al., 1994 (17)	United Kingdom	Randomized, double-blind, placebo-controlled trial	56 postmenopausal women (35 completed the study) with >3 hot flashes daily Age, 45–67 y
Ginseng			
Wiklund et al., 1999 (18)	Sweden	Randomized, double-blind, placebo-controlled multicenter trial	384 postmenopausal women (379 completed the study) with ≥6 hot flashes during 3 of 7 days Age, 45–65 y
Chinese herb mixture			
Davis et al., 2001 (19)	Australia	Randomized, double-blind, placebo-controlled trial	78 postmenopausal women (55 completed the study) with ≥14 hot flashes or night sweats weekly Age, 45–70 y

*CGI = Clinical Global Impression Scale; FSH = follicle-stimulating hormone; HAM-A = Hamilton Anxiety Scale; HDL = high-density lipoprotein; LH = luteinizing hormone; SDS = Self-Assessment Depression Scale; SHBG = sex hormone–binding globulin; VAS = visual analogue scale; VMI = vaginal maturation index; WHQ = Women's Health Questionnaire.

† Manufacturers: Ginsana (G115), Pharmaton, Lugano, Switzerland; Ovestin, Organon, West Orange, New Jersey; Presomen, Solvay Pharmaceuticals, Marietta, Georgia; Promensil, Novogen, Sydney, Australia; Remifemin, GlaxoSmithKline, Pittsburgh, Pennsylvania; Trisequens, Novo Nordisk, Princeton, New Jersey.

‡ Comments are italicized.

ginseng (*Panax ginseng* and other *Panax* species), evening primrose oil (*Oenethera biennis*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense)*, and licorice (*Glycyrrhiza glabra*). We identified 10 trials of herbs (Table 1) (10–19). Most studies found no significant changes in primary outcome measures. However, these studies were small, of short duration, and far from sufficient to yield definitive conclusions.

The most studied and perhaps most popular herb is black cohosh, traditionally used by Native Americans for

Table 1—**Continued**

Treatment, Dose, and Duration†	Outcome Measures	Findings and Comments‡
Remifemin tablets (40 mg/d herbal extract) vs. placebo Duration, 2 mo	Frequency and intensity of hot flashes; menopause symptom index (6 symptoms); global rating of health scale; FSH and LH levels	No significant difference between groups in frequency and intensity of hot flashes (decreased in both groups); significantly greater decrease in sweating in treatment group than in placebo group ($P = 0.04$); no changes in global rating scale or FSH and LH levels *Study duration was short; medication-induced hot flashes are more difficult to treat than naturally occurring hot flashes*
Remifemin (liquid) (40 drops twice daily) vs. conjugated estrogens (0.25 mg/d) vs. diazepam (2 mg/d) Duration, 3 mo	Kupperman index scores (modified 5 symptoms); HAM-A; SDS; CGI; VMI	Kupperman index, HAM-A, SDS, and CGI showed "highly significant reductions" with all three therapies; VMI: "trend towards estrogenic stimulation" for Remifemin and estrogen *No statistical calculations reported*
Remifemin tablets (4 mg twice daily) vs. conjugated estrogens (0.625 mg/d) vs. placebo Duration, 3 mo	Kupperman index scores (9 symptoms); hot flashes; HAM-A; VMI	Significant improvement in Kupperman index score, HAM-A ($P < 0.001$), and VMI ($P < 0.01$); no change in estrogen or placebo groups; hot flashes decreased from 4.9 to 0.7/d in Remifemin group, 5.2 to 3.2 in estrogen group, and 5.1 to 3.1 in placebo group (significance not indicated) *Lack of effect with estrogen calls other findings into question*
Remifemin tablets (4 mg of triterpene glycosides twice daily) vs. estriol (Ovestin, 1 mg/d) vs. conjugated estrogens (Presomen, 1.25 mg/d) vs. estrogen/progesterone combination (Trisequens) Duration, 6 mo	Kupperman index scores (modified 17 symptoms); LH and FSH levels	Kupperman index scores improved in all groups ($P = 0.01$); no differences among treatment groups; no changes in LH and FSH levels
Promensil (40 mg of total isoflavones) vs. placebo Duration, 7.5 mo (12 wk, then 4-wk washout, then 14 wk)	Frequency of hot flashes; symptoms (Greene menopause scale); LH, FSH, estradiol, and SHBG levels; VMI; endometrial thickness (evaluated using ultrasonography)	No difference between groups in frequency of hot flashes (decreased in both groups) or other outcome measures *Study too short to adequately assess estrogenic effects on endometrium; adverse events not mentioned*
Promensil (40 mg of total isoflavones) vs. Promensil (160 mg of isoflavones) vs. placebo Duration, 3 mo	Frequency of hot flashes; symptoms (Greene menopause scale); FSH, SHBG, and HDL cholesterol levels; VMI	No difference among groups in frequency of hot flashes (decreased in all groups), VMI, FSH level, or SHBG level; HDL cholesterol level increased significantly (18%) ($P = 0.038$) in 40-mg Promensil group only *Although total cholesterol and triglyceride tests were done, results were not reported (blood was collected when patients were not fasting)*
Dong quai (3 capsules 3 times/d; equivalent 4.5 g of dong quai root/d; standardized to 0.5 mg/kg ferulic acid) vs. placebo Duration, 6 mo	Kupperman index score; vasomotor flushes; endometrial thickness; VMI; vaginal dryness; estradiol, estrone, and SHBG levels	No difference between groups in Kupperman index scores (decreased significantly in both groups), number of hot flashes, VMI, or endometrial thickness *Dong quai is not considered estrogenic and not usually prescribed alone in Traditional Chinese Medicine*
Evening primrose oil (2000 mg with 20 mg of vitamin E) twice daily vs. placebo Duration, 6 mo	Hot flashes or sweating episodes	Frequency of daytime hot flashes decreased in placebo but not evening primrose oil group; no difference between groups in frequency of nighttime hot flashes (decreased in both groups)
Ginseng (Ginsana containing 100 mg of standardized extract G115) Duration, 4 mo (2-wk run-in, 14-wk treatment)	Hot flashes and other symptoms (VAS); Psychological General Well-Being Index; WHQ (measures of quality of life); FSH and estradiol levels; endometrial thickness (evaluated using ultrasonography); VMI	No significant differences between groups in hot flashes (assessed as part of WHQ) or any main outcome measures
Chinese herbal formula (daily dose of *Rehmannia glutinosa*, 15 g; *Cornus officinalis*, 10 g; *Dioscorea opposita*, 12 g; *Alisma orientalis*, 8 g; *Paeonia suffruticosa*, 8 g; *Poria cocos*, 12 g; *Citrus reticulata*, 5 g; *Lycium chinense*, 20 g; *Albizzia julibrissin*, 15 g; *Ziziphus jujuba*, 10 g; *Eclipta prostrata*, 15 g; *Ligustrum lucidum*, 10 g) vs. bitter placebo Duration, 3 mo	Hot flashes and night sweats (by daily diary); Menopause-Specific Quality-of-Life Questionnaire scores; urinary phytoestrogen excretion	No difference between groups in frequency of vasomotor symptoms or Menopause-Specific Quality-of-Life Questionnaire score (both decreased in both groups); urinary phytoestrogen levels did not change in either group

gynecologic and other conditions. Almost all clinical studies of black cohosh have used the standardized product Remifemin (GlaxoSmithKline, Pittsburgh, Pennsylvania); however, the formulation and the dosage have changed over time. One of four randomized, controlled trials of black cohosh for hot flashes was placebo controlled (10), one used both a treatment and placebo control (12), and two were treatment controlled (11, 13). Three of the four trials found black cohosh to be beneficial for treating hot flashes.

Table 2. **Soy and Soy Extracts for Hot Flashes***

Study, Year (Reference)	Country	Study Design	Patient Characteristics and Age
Van Patten et al., 2002 (34)	Canada	Randomized, double-blind, placebo-controlled trial	157 postmenopausal women (123 completed the study) with breast cancer and hot flashes
Han et al., 2002 (35)	Brazil	Randomized, double-blind, placebo-controlled trial	82 postmenopausal women (80 completed the study) with hot flashes Age, 45–55 y
St. Germain et al., 2001 (36)	United States	Randomized, double-blind, placebo-controlled trial	91 perimenopausal women (69 completed the study) with ≥10 hot flashes weekly Age, 42–62 y
Scambia et al., 2000 (37)	Italy	Randomized, double-blind, placebo-controlled trial	39 postmenopausal women (22 completed the study); included surgical and early menopause Age, 29–63 y
Quella et al., 2000 (38)	United States	Randomized, double-blind, placebo-controlled, crossover trial	177 women (149 completed the study) with history of breast cancer and <14 hot flashes weekly; most patients were receiving tamoxifen or raloxifene Age, ≥18 y
Upmalis et al., 2000 (39)	United States	Randomized, double-blind, placebo-controlled, multicenter trial	177 postmenopausal women (117 completed the study) with ≥5 hot flashes daily Age, ≥50 y
Washburn et al., 1999 (40)	United States	Randomized, double-blind, placebo-controlled, crossover trial	51 perimenopausal women (42 completed the study) with >1 hot flash daily Age, 45–55 y
Albertazzi et al., 1998 (41)	Italy	Randomized, double-blind, placebo-controlled multicenter trial	104 postmenopausal women (79 completed the study) with ≥7 hot flashes daily Age, 45–62 y
Dalais et al., 1998 (42)	Australia	Randomized, double-blind, placebo-controlled, crossover trial	52 postmenopausal women (44 completed the study) with ≥14 hot flashes weekly Age, 45–65 y
Brzezinski et al., 1997 (43)	Israel	Randomized, placebo-controlled, unblinded trial	145 peri- and postmenopausal women (114 completed the study) with ≥1 climacteric symptom Age, 43–65 y
Murkies et al., 1995 (44)	Australia	Randomized, placebo-controlled trial	58 postmenopausal women (47 completed the study) with >14 hot flashes weekly Age, 30–70 y
Baird et al., 1995 (45)	United States	Randomized, controlled trial	97 postmenopausal women (91 completed the study) Age, 45–65 y

*FSH = follicle-stimulating hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LH = luteinizing hormone; SHBG = sex hormone–binding globulin; VMI = vaginal maturation index.

† Manufacturer: SOYSELECT, Indena, Settala, Milan, Italy.

‡ Comments are italicized.

Neither the identity of active compounds nor the mechanism of action of black cohosh is known. Although formononetin, an estrogenic isoflavone, was reported to have been isolated from black cohosh extract (20), another study found no formononetin in black cohosh extract (21). In addition, a recent systematic examination of extracts of

Table 2—**Continued**

Treatment, Dose, and Duration†	Outcome Measures	Findings and Comments‡
Soy beverage (90 mg of isoflavones/d) vs. control (rice beverage) Duration, 12 wk	Hot flash frequency and hot flash score (number × severity)	No difference between groups; hot flash scores decreased in both the soy group (30%) and the control group (40%). More gastrointestinal effects were reported in the soy group
Capsules containing daily dose of 150.9 mg of soy protein and 100 mg of isoflavones (69.9 mg of genistein, 18.6 mg of daidzein, 11.4 mg of glycitein) Duration, 4 mo	Kupperman index score; lipids; body mass index; blood pressure; glucose, FSH, LH, and 17β-estradiol levels	Compared with placebo, treatment decreased menopausal symptoms ($P < 0.01$), decreased total cholesterol and LDL levels ($P < 0.01$), and increased 17β-estradiol levels (from 9 ± 1.2 pg/mL to 19 ± 2.2 pg/mL; $P < 0.001$). No effects on other outcome measures *This was the only study that found increased estradiol levels*
40 g/d of isoflavone-rich soy protein (80.4 mg aglycones) vs. 40 g/d of isoflavone-poor soy protein (4.4 mg/d of aglycones) vs. 40 mg/d of control (whey protein) Duration, 24 wk	Frequency and severity of hot flashes and night sweats; insomnia; fatigue; mood swings; vaginal dryness and other menopausal symptoms	No significant difference between groups in frequency or severity of hot flashes or night sweats at 12 or 24 weeks (hot flashes decreased in all groups); no changes in other outcome measures *Longest study to date; 6-wk data not presented; sporadic symptoms throughout the study (menopausal transition)*
Standardized soy extract (SOYSELECT: 400 mg/d [50 mg/d of isoflavones]) vs. placebo. After 6 wk, conjugated estrogens (0.625 mg/d) were added to treatment; after 8 wk, soy was discontinued and medroxyprogesterone acetate (10 mg/d) was added to the conjugated estrogens Duration, 12 wk (6 wk treatment, 4-wk treatment plus conjugated estrogens; 2-wk conjugated estrogens plus medroxyprogesterone acetate)	Frequency and severity of hot flashes; Greene menopause scale; VMI; endometrial thickness; pulsatility index of uterine artery; total cholesterol, HDL, LDL, triglyceride, FSH, and LH levels	Compared with placebo, treatment decreased frequency and severity of hot flashes ($P < 0.01$ and $P < 0.001$) at 6 wk; soy caused no changes in other outcome measures; conjugated estrogens caused predictable estrogenic changes in both groups
Soy tablets containing daily dose of 150 mg of isoflavones vs. placebo Duration, 8 wk (each phase, 4 wk)	Frequency and intensity of hot flashes and hot flash score (frequency × severity)	No difference between groups in hot flash score or frequency (frequency of hot flashes decreased in both groups); patients did not prefer soy over placebo
Standardized soy isoflavone extract containing 50 mg of genistein plus daidzein daily vs. placebo Duration, 12 wk	Frequency and severity of hot flashes and night sweats; SHBG and FSH levels; VMI; endometrial thickness (evaluated using ultrasonography); *N*-telopeptide; quality-of-life measures; total cholesterol, LDL, HDL, and triglyceride levels	Compared with placebo, treatment reduced frequency of hot flashes at 6 wk ($P = 0.03$); at 12 wk, treatment reduced severity of hot flashes and night sweats ($P = 0.01$), but not frequency of hot flashes or night sweats; no changes in other outcome measures *Relative lack of soy protein in supplement*
20 g of soy protein powder daily (34 mg of isoflavones) in single or split doses vs. control (isoflavone-free carbohydrate) Duration, 18 wk (each phase lasted 6 wk)	Frequency and severity of hot flashes; estrogen symptom score (including hot flashes, vaginal dryness, sleep disturbances); total cholesterol, LDL, HDL, and triglyceride levels; blood pressure	Severity of hot flashes ($P < 0.001$) and estrogen symptom score ($P < 0.05$) improved only in split-dose soy group; no differences among groups in frequency of hot flashes; compared with control, treatment (for both soy groups) decreased total cholesterol and LDL levels ($P < 0.05$); no changes in HDL or triglyceride levels; diastolic blood pressure decreased ($P < 0.01$) only in split-dose soy group *No washout between crossover; baseline number of hot flashes not reported*
60 g of isolated soy protein powder daily (40 g of protein, 76 mg of isoflavones [aglycones]) vs. control (isoflavone-free casein powder containing 40 g of protein) Duration, 12 wk	Frequency and severity of hot flashes; Kupperman index scores; blood pressure	Compared with control, treatment significantly reduced frequency of hot flashes (45% vs. 31%) at 12 wk ($P < 0.01$); no change in Kupperman index score
45 g/d (in form of bread) of soy grits (53 mg/d isoflavones) or linseed (flaxseed) vs. control (wheat meal) Duration, 28 wk (each phase lasted 12 wk, 4-wk washout)	Frequency of hot flashes; VMI; bone mineral content; bone mineral density	Compared with baseline, linseed and wheat (but not soy) decreased frequency of hot flashes; only soy improved VMI (increase of 103%) ($P < 0.04$) and bone mineral content (increase of 5.2%) ($P = 0.03$); no changes in bone mineral density *Increased bone mineral content in soy group over short time is of note*
Phytoestrogen-rich diet containing soybean food and flaxseed (1/4 caloric intake) vs. control (normal diet) Duration, 12 wk	Menopause symptom questionnaire; estradiol, LH, FSH, SHBG, and serum phytoestrogen levels	No differences between groups in menopause symptom questionnaire scores, which decreased in both groups; compared with control, treatment significantly increased SHBG levels ($P < 0.003$) and significantly decreased vaginal dryness ($P = 0.005$) and hot flash "severity score" ($P = 0.004$) assessed as part of the menopause symptom questionnaire *Report states that estradiol level did not change significantly; however, table shows estradiol decreased in both groups; no report of 6-wk data*
45 g/d of soy flour vs. 45 g/d of wheat flour Duration, 12 wk	Frequency of hot flashes and hot flash score (frequency × severity); other menopausal symptoms; VMI; lipid and FSH levels	No significant differences between groups in menopausal symptoms, frequency of hot flashes or hot flash score (decreased in both groups), or other outcome measures; no change in VMI or lipids; compared with baseline, FSH level decreased significantly only in the control group
Soy diet (1/3 caloric intake; estimated 165 mg/d of isoflavones) vs. control (usual diet) Duration, 4 wk	VMI; LH, FSH, and SHBG levels	No significant changes in any outcome measures *Hot flashes not measured; trial very short in duration*

black cohosh collected from 13 locations in the eastern United States as well as Remifemin also found no formononetin in any sample (22). Thus, other compounds must be responsible for its biological activity. Small amounts of biochanin, another isoflavone, have been isolated from *C. racemosa* roots (23). Other candidates for the biological activity of black cohosh include triterpene glycosides, organic acids, and esters.

Black cohosh is not usually used on a long-term basis, and no clinical trials have lasted for more than 6 months. This is of concern because women using this product for "natural" hormone replacement therapy may take it for years. There are no published data from human trials about long-term safety, particularly regarding endometrial or breast stimulation. Effects on vaginal epithelium are inconclusive; two of five randomized, controlled trials that examined estrogenic effect on vaginal epithelium reported a stimulatory effect (11, 12). In vitro and in vivo studies are not consistent or sufficient. Although black cohosh may be useful for menopausal symptoms, long-term use cannot be presumed to be safe until appropriate safety studies are conducted.

Red clover contains the phytoestrogens formononetin, biochanin A, daidzein, and genistein (24). Two small, 3-month clinical trials conducted in Australia reported no significant benefit of red clover extract for hot flashes (14, 15) (**Table 1**). Several larger trials are in progress. Red clover, a Native American herb, has not been traditionally used on a long-term basis for hot flashes, and it is unknown whether long-term use would have an estrogenic effect on the breast or endometrium.

Dong quai, a Chinese herb traditionally prescribed as a tonic for women, is most commonly used as part of a mixture. It is sold in the United States for use alone or as part of newly formulated, nontraditional herbal combinations. One trial of dong quai found no benefit for hot flashes (16) (**Table 1**). It would be valuable to study Traditional Chinese Medicine (TCM) formulas, prescribed in accordance with TCM diagnostic methods. Dong quai does not contain the typically reported phytoestrogens, and the data on stimulation of estrogen receptor–positive breast cancer cells or binding to estrogen receptors (25, 26) are conflicting. Dong quai contains coumarins and can cause bleeding when administered concurrently with warfarin (27); the furocoumarins contained in dong quai can cause photosensitization (24).

Oil of evening primrose, a good source of the prostaglandin E_1 precursor γ-linolenic acid, was evaluated for hot flashes in one trial; no differences were found between a group of patients using evening primrose oil and a placebo group (17). Single-dose studies are difficult to evaluate when optimum dose and duration of treatments are unknown. Evening primrose oil is a benign treatment.

Ginseng has been used as a tonic for centuries in Asia. One trial found no benefit of ginseng over placebo for menopausal symptoms and quality-of-life measures, although there were positive effects on mood (18). Case reports link ingestion of ginseng with postmenopausal bleeding (28, 29); one case of postmenopausal bleeding occurred after topical use of a ginseng-containing face cream (30). Ginseng also reduced the international normalized ratio in one patient receiving warfarin therapy (27).

In summary, of the herbs that have been tested for hot flashes, only black cohosh has shown a beneficial effect. Questions remain about the long-term safety of most herbs.

Dietary Phytoestrogens

Many food plants contain phytoestrogens, primarily phenolic (rather than steroidal) compounds that include isoflavones, lignans, and coumestans. Isoflavone precursors are found in soy and other types of beans, clover, and alfalfa. Lignan precursors are found in whole grains, seeds (especially flaxseed [linseed]), fruits, vegetables, rye, millet, and legumes (31). Intestinal bacteria convert plant lignans to mammalian lignans (enterolactone and enterodiol) and convert conjugated isoflavones to unconjugated active isoflavones (genistein, daidzein, and equol). Phytoestrogens are estrogenic, and, thus, diet may modulate endocrine actions in the body. High dietary intake of soy products in Japan, China, and Korea has been proposed as one reason for the lower prevalence of menopausal symptoms reported in those countries (32, 33). Soy foods have become popular in the United States for treating hot flashes, despite few strong supporting clinical studies.

We identified 11 clinical trials that examined soy or isoflavone supplementation for hot flashes (**Table 2**) (34–44); one additional study of soy for menopausal women examined vaginal epithelium rather than hot flashes (45). Products studied ranged from soy foods to purified isoflavone preparations. Only 3 of 8 studies with treatment phases that lasted for more than 6 weeks showed significant improvement in hot flashes at the end of the study (35, 41, 43). The longest study to date showed no benefit for hot flashes (or other symptoms) at 24 weeks (36). Comparisons are difficult because of variations in product, dosage, scoring systems for symptoms of hot flashes, and the menopausal status of patients. Published data show only modest effects (primarily on the severity of hot flashes), and most benefits disappeared after 6 weeks (for hot flashes, even 3 months is barely adequate to appropriately assess efficacy). It is of interest that in most of these studies, symptoms decreased in all groups—often as much as 50% to 60% in placebo as well as treatment groups. Studies of longer duration must be done to determine whether this placebo effect would have declined over time in any or all groups. Additional studies of menopausal symptoms are warranted to differentiate among whole foods, soy protein, and isoflavone extracts. Soy foods have been a staple in Asian cuisine for thousands of years and are presumed safe. Supplementing the diet with beans or bean products is a benign intervention. No such presumption of safety can be made for the isolated, often high-dose, isoflavones that are currently sold over the counter.

Vitamin E

Vitamin E, recommended in many popular books for hot flashes, was the subject of poorly controlled studies in the 1940s and 1950s. A double-blind, 3-year study in 1953 compared vitamin E (50 to 100 mg/d) with two estrogen preparations, phenobarbital, and a placebo in 658 women (46). On an 11-symptom menopause index (hot flashes were not analyzed separately), more than 90% of women treated with estrogen and 43% of women treated with phenobarbital responded; vitamin E was no more effective (26%) than placebo (33%). A recent randomized, placebo-controlled crossover study tested vitamin E (400 IU vitamin E succinate twice daily) in 125 breast cancer survivors with at least 14 hot flashes weekly (47). After 4 weeks, vitamin E was associated with one less hot flash daily when compared with placebo. The difference was statistically but not clinically significant; patients did not prefer vitamin E to placebo.

Acupuncture

In a study of the effects of acupuncture on hot flashes, 24 menopausal women were randomly assigned to either an electroacupuncture group (electrical stimulation of acupuncture needles at standardized points) or to a control group (shallow acupuncture needle insertion at the same points) (48). Women were treated twice weekly for 2 weeks and then weekly for an additional 6 weeks. Hot flashes and Kupperman index scores decreased significantly ($P < 0.05$) in both groups, and there were no differences between groups. In addition, sleep dysfunction scale scores did not change. Because shallow needle insertion at correct acupuncture points would be expected to have some effect, the chosen control may have been suboptimal. Acupuncture causes tissue trauma occasionally and serious complications (including pneumothorax and cardiac tamponade) rarely. The most common serious complication has been the transmission of hepatitis viruses or other infections agents via inadequately sterilized needles (49). Disposable needles, the standard of care in the United States, obviate this concern.

Behavioral Therapies

Few studies have examined behavioral methods for moderating hot flashes. One study compared paced respiration (slow, deep breathing) with progressive muscle relaxation or nontherapeutic α-wave electroencephalographic biofeedback (control) in 33 postmenopausal women (50). Paced respiration training for 4 months significantly reduced the frequency of hot flashes by 39% ($P < 0.02$); progressive muscle relaxation training and the control intervention had no significant effect. In a more recent trial by the same investigators, 24 postmenopausal women with at least five hot flashes daily were randomly assigned to either paced respiration or biofeedback control (51). Paced respiration decreased hot flashes significantly (44% [$P < 0.001$]); no change occurred in the control group. No adverse effects were noted.

A randomized, controlled, 7-week study of the relaxation response technique involved 45 women (33 completed the study) between 44 and 66 years of age who were experiencing at least five hot flashes daily (52). The women were randomly assigned to a relaxation response group, a reading group, or a symptom-charting (control) group. The relaxation group was instructed in relaxation response techniques and asked to practice 20 minutes daily; the reading group read leisure material for 20 minutes daily. Compared to baseline, the frequency of hot flashes did not change in any group; the intensity of hot flashes decreased significantly only in the relaxation group ($P < 0.05$). State anxiety did not change in any group; trait anxiety (assessed by using the Spielberger State-Trait Anxiety Inventory) decreased significantly only in the relaxation group ($P < 0.04$). Behavioral therapies seem to be safe; an explanation for treatment effects is needed.

Wild Yam and Progesterone Creams

Topical wild yam (*Dioscorea villosa*) and "natural" (micronized) progesterone creams have been promoted for hot flashes as well as many other conditions (53). Wild yam preparations contain diosgenin, which can be converted to progesterone in a laboratory but not in the human body. A double-blind, placebo-controlled crossover trial tested wild yam cream against placebo for 3 months in 23 symptomatic menopausal women (54). The treatment and placebo groups did not differ in hot flashes or night sweats (both improved slightly in both groups). There were no changes from baseline in body weight; blood pressure; or levels of serum estradiol, serum or salivary progesterone, total cholesterol, triglyceride, high-density lipoprotein cholesterol, follicle-stimulating hormone, and glucose.

Pharmacologically active progesterone creams are also sold over the counter. A randomized, double-blind, placebo-controlled trial on the effect of progesterone cream on bone examined hot flashes as a secondary outcome (55). Healthy postmenopausal women ($n = 102$) applied one-quarter teaspoon of progesterone cream (20 mg of progesterone) or placebo daily for 1 year. The women also received daily multivitamins and calcium (1200 mg daily). The treatment did not affect bone, but among patients who initially reported hot flashes, 5 of 26 women in the control group compared with 25 of 30 women in the treatment group reported "improvement"; this difference was significant ($P < 0.001$). Eight women treated with progesterone cream had vaginal spotting. Endometrial biopsy revealed proliferative endometrium in one woman; biopsies for the other seven women retrieved insufficient tissue for diagnosis. The induction of postmenopausal bleeding is worrisome and should be explored further.

Consumers sometimes use transdermal progesterone creams as the progestin component of hormone replacement therapy; however, three studies have shown that serum levels of progesterone after application of transdermal creams are insufficient to prevent estrogenic stimulation of the endometrium (56–58).

DISCUSSION

Hot flashes are the primary symptom for which menopausal women seek "natural" treatments. In well-designed but small trials, vitamin E, red clover, evening primrose oil, and dong quai were ineffective for hot flashes. Several controlled trials supported the use of black cohosh for menopausal symptoms; the two placebo-controlled studies that specifically examined hot flashes found opposite results. As herbs usually take longer than estrogen therapy to work, the typical 3-month pharmaceutical trial model may be too short to accurately assess the value of an herb (in all studies of herbs, duration of treatment is important). Safety data on long-term use of herbs are inadequate. Because of the popularity of black cohosh, it is extremely important to elucidate both its benefits and potential risks (especially on stimulation of endometrial or breast tissue). Behavioral approaches (such as paced respiration) are safe, have shown some initial promise, and deserve further study. There are sufficient data to discourage the use of natural progesterone cream as the progestational component of hormone replacement therapy or for the treatment of osteoporosis.

Not all herbs and dietary supplements are risk-free. Many herbs are being promoted for nontraditional uses. Newly formulated combination herbal products (often containing novel mixtures or subtherapeutic doses) should be avoided until research data are available; currently, no safety or efficacy data on such combinations have been published. The subtherapeutic doses often found in such preparations may render them harmless, but even that cannot be counted on. Although plant foods are presumed to be safe, the isolated, often concentrated components have not been tested for long-term use. Furthermore, because of the lack of adequate product quality control in the United States, it is difficult to identify the reliable supplement brands. The number of herbal products in the U.S. marketplace is growing rapidly, and recommended dosages are increasing without research supporting the need for these larger doses.

Health care providers and consumers should be aware that despite the potential usefulness of many CAM therapies, scientific research is limited. Product advertising hype far exceeds scientific knowledge, and scientific evaluation is essential to enable an informed choice among treatments. The popularity of CAM therapies and their therapeutic potential necessitate definitive safety and efficacy studies. Because herbs, vitamins, and other natural products cannot be patented, industry-sponsored research will remain limited. Federal and alternative funding sources must bridge this gap.

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2002–2003 Series: Update Sessions from ACP–ASIM's 2002 Annual Session
David A. Cramer, MD, and Paul T. Kefalides, MD, Co-Editors

Update in Hospital Medicine

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This Update summarizes 12 articles published in 2001 that are important to primary inpatient physicians. To select these papers, we scanned 11 major medical journals and *ACP Journal Club* and informally polled experts in our geographic regions to find articles that we believe are methodologically sound and will have the greatest impact on hospital medicine. The research is grouped into seven categories: quality improvement, invasive procedures, pulmonary diseases, infectious diseases, cardiology, endocrinology, and critical care.

Quality Improvement

Computerized Reminder System Increased Ordering of Preventive Care Measures

Dexter PR, Perkins S, Overhage JM, et al. A computerized reminder system to increase the use of preventive care for hospitalized patients. N Engl J Med. 2001;345:965-70. [PMID: 11575289]

Dexter and colleagues asked whether the use of a computer reminder system for inpatient orders could improve ordering rates for the following preventive health measures: pneumococcal vaccination, influenza vaccination, prophylactic aspirin use in patients with cardiovascular disease, and subcutaneous heparin.

This randomized, controlled trial followed the orders written by eight teams of general medicine residents for 18 months. Resident physicians were randomly assigned to an intervention group or a control group, and efforts were made to maintain them in their assigned groups despite monthly rotations in and out of inpatient general medicine. The residents in the intervention group received reminders on their computer screens to give vaccines or specific preventive medicines whenever certain criteria were met. Clinical information derived from pharmacy and radiology records, as well as data gathered by a research assistant, was compiled to generate the computerized reminders.

Throughout the study period, 6371 patients accounted for 10 065 admissions, and 54% of these patients were eligible for at least one intervention. Patient characteristics did not significantly differ between the intervention and control groups. Two hundred two physicians participated in the study; 47% remained solely in the intervention group during the study period, 38% stayed in the control group, and 13.9% were in both groups. Pneumococcal vaccination was given to 35.8% of patients cared for by the residents who received computer reminders but only 0.8% of patients in the control group ($P < 0.001$); 51.4% of the intervention group received influenza vaccine compared with only 1% of the control group ($P < 0.001$). On average, the physicians viewed the reminders four times.

The computer order entry system in this study led to impressive gains in ordering rates. These rates did not approach 100%, however, perhaps because the physicians had details of the patients' conditions that were unavailable to the computer system. In a 1996 study by these same investigators, the computer suggested but did not automatically enter orders, and the interface was less graphically appealing (1). In that study, physician behavior did not change, suggesting that programming the computer to place the order unless manually overridden by the physician maximizes fulfillment of the preventive health initiatives. Although the program tested in the 2001 study is expensive and requires data collection and synthesis, it had dramatic results and its use should grow as hospitals update their information systems.

Invasive Procedures

Femoral Line Placement Should Be Avoided

Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA. 2001;286:700-7. [PMID: 11495620]

Published complication rates for femoral and subclavian central venous catheters vary widely, and until last year no randomized trials had compared these catheters directly. In Merrer and colleagues' randomized, controlled trial, patients were enrolled at eight intensive care units at four university and four community hospitals in France. Staff physicians or supervised residents inserted femoral and subclavian lines. Eligible patients were 18 years or older and were receiving their first venous catheter of the admission. The investigators excluded patients requiring emergency catheter placement and those with coagulopathy, morbid obesity, severe hypoxemia, and other anatomic limitations. The physicians were permitted to switch from either side if the insertion was unsuccessful. Although the report indicates that sterile barrier precautions were taken, the authors did not specify whether the physicians had

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For author affiliations, see end of text.
For a list of related articles, see Appendix at www.annals.org.

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formal training in antiseptic technique or whether antiseptic technique was standardized. The site preparation and the frequency of the dressing changes were also allowed to vary. The catheters could be used for any purpose, including the infusion of vasopressors, blood products, or antibiotics. Both major and minor complications were tabulated. Pneumothorax, hematoma requiring intervention, complete vascular thrombosis, and catheter-related sepsis were considered major complications.

Of 1700 eligible patients, 289 (18%) were enrolled; 145 received femoral catheters and 144 had subclavian lines. Patient characteristics did not significantly differ between groups. During the study period, subclavian catheters were in place longer than femoral catheters (mean, 11.0 days vs. 9.3 days; $P = 0.01$). A similar percentage of patients in each group had mechanical complications: 17.3% of the femoral group and 18.8% of the subclavian group ($P > 0.2$). Two femoral hematomas and four pneumothoraces occurred. In a bivariate analysis of variables that contributed to mechanical complications, catheter insertion at night, time required for catheter insertion, overall duration of placement, and placement at two of the participating centers were independent predictors of mechanical complications (Table 1). Seven major thrombotic complications occurred in the femoral group and none occurred in the subclavian group ($P = 0.1$). A catheter tip was cultured for 93% of all patients; 20% of the femoral group and 4.5% of the subclavian group had infectious complications. Most of the femoral infections were due to colonization. The total number of major complications was 15 in the femoral group and 7 in the subclavian group, and the number needed to treat for harm in 1 patient was 18. The absolute risk reduction for major complications with subclavian versus femoral site was 6% (95% CI, 0.2% to 12%).

In summary, femoral lines were associated with a significantly greater rate of infectious and thrombotic complications. The femoral site should be avoided if possible. It would be valuable to include internal jugular lines in a future comparison of central venous catheter sites.

Table 1. **Independent Risk Factors for Complications of Central Line Placement**

Risk Factors	Odds Ratio (95% CI)	*P* Value
For mechanical complications*		
Time required for insertion	1.05 (1.03–1.08)	<0.001
Insertion at two of the centers	4.52 (1.81–11.23)	0.001
Insertion at night	2.06 (1.04–4.08)	0.03
For infectious complication		
Femoral catheterization	4.83 (1.96–11.93)†	<0.001
For thrombotic complication		
Femoral catheterization	14.42 (3.33–62.57)	<0.001

* Mechanical complications were arterial puncture, pneumothorax, hemothorax or mediastinal hematoma, misplacement of catheter tip, hematoma or bleeding, and air embolism.

† Hazard ratio.

Pulmonary Diseases

Spiral Computed Tomography Is Not Ready for Use as a Solitary Test To Diagnose Pulmonary Embolism

Perrier A, Howarth N, Didier D, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med. 2001;135:88-97. [PMID: 11453707]

In previous studies that examined helical computed tomography (CT) in pulmonary embolism, the methods varied and the results were inconsistent; the reported sensitivity for detecting pulmonary embolism ranged from 53% to 100%. Perrier and colleagues sought to determine the operating characteristics of helical CT in the diagnosis of pulmonary embolism. Perrier and colleagues followed a cohort of 1108 consecutive patients who presented to the emergency department of University Hospital of Geneva in Switzerland with clinical suspicion of pulmonary embolism. All patients were at least 16 years of age and had elevated D-dimer levels (>500 μg/L) on an enzyme-linked immunosorbent assay. Of the 722 patients with elevated D-dimer levels, 38% were excluded because of contraindications to CT, technical difficulties, or incomplete follow-up. The clinical and demographic variables did not significantly differ between the excluded patients and the study participants. After exclusions, 299 patients were available for the analysis. Lower-extremity Doppler was done on the first day. Pulmonary embolism was diagnosed by a positive pulmonary arteriogram, a high-probability ventilation–perfusion scan, or an ultrasound showing deep venous thrombosis in the context of clinical suspicion for pulmonary embolism. Helical CT was also performed, but the results were withheld from the clinicians managing the patients; blinded radiologists read the scans 3 months later at follow-up. Information on clinical events, such as deep venous thrombosis, embolism, and bleeding, was available for all patients during the 3-month follow-up.

Of the 287 patients with conclusive CT scans, 116 were positive for pulmonary embolism and 71 were negative. The sensitivity of helical CT was 70% (CI, 62% to 78%) and the specificity was 91% (CI, 86% to 95%). In 97% of the 35 patients with false-negative helical CT scans, embolism was detected by ventilation–perfusion scanning, ultrasonography, or angiography. No pulmonary embolisms were diagnosed in the low-risk cohort (defined by a D-dimer value < 500 μg/L), and the interobserver agreement among the three CT scan readers was excellent (nonweighted $\kappa = 0.823$ to 0.902). After low-risk patients were excluded, the prevalence of disease was 38%, slightly higher than the 28% reported in the Prospective Investigation of Pulmonary Embolism Diagnosis Criteria (PIOPED) study (2).

Because of low sensitivity, helical CT is currently inadequate as a solitary test to rule out pulmonary embolism, and it is only moderately effective in helping clinicians rule in the disease. Moreover, its cost-effectiveness is still unclear. Furthermore, because of the way this study was designed, the results apply only to patients screened with a D-dimer assay.

Infectious Diseases

History and Physical Examination Can Predict Risk for Lumbar Puncture in Patients with Meningitis

Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med. 2001;345:1727-33. [PMID: 11742046]

This study may have been partly motivated by the congestion in emergency departments and the delays that result from awaiting interpretation of CT scans. Researchers at Yale New Haven Hospital in New Haven, Connecticut, asked whether history and physical examination findings in patients with suspected bacterial meningitis could predict which patients would have a normal CT scan before lumbar puncture. If clinical criteria could help select patients for quick lumbar puncture, delays could be reduced and many scans would be unnecessary.

Of 511 consecutively identified patients seen in the emergency department, 301 were enrolled. All participants were at least 16 years of age and showed clinical signs of meningitis. Socioeconomic status, comorbidity via the Charleston Comorbidity Index, laboratory findings, and neurologic abnormalities were tabulated at baseline. The emergency department physician decided whether to obtain a CT scan. Almost all patients received lumbar punctures, and their clinical status was evaluated after the first week of study. Staff neuroradiologists, who were blinded to the clinical presentations, read the scans. The scans were reviewed for the presence of any abnormality or mass effect.

The median age of the cohort was 40 years, and the typical presentation included headache, fever, and a normal level of consciousness. However, about 15% of the patients were older than 60 years of age, and 25% were HIV positive. Fifty percent were white, 30% were black, and 20% were Hispanic. Focal neurologic deficits were noted in 17% of the patients according to the Modified National Institutes of Health Stroke Scale.

Of the 301 patients enrolled, 66 patients did not have a CT scan but did undergo lumbar puncture without complication. Of the 235 patients who underwent CT, 76% had normal scans and 24% had abnormal scans. Through regression analysis, the investigators determined which variables separated the two groups. Only 5% of the patients had mass effect on CT scan, and only 4 patients overall did not undergo a lumbar puncture because of the CT results.

In the regression analysis, four variables were significantly associated with abnormal CT scans: age older than 60 years ($P < 0.001$), immunocompromised state ($P = 0.01$), a history of central nervous system disease ($P < 0.001$), and seizure in the preceding week ($P < 0.001$). Significant physical findings were an abnormal level of consciousness ($P < 0.001$); inability to answer two consecutive questions ($P < 0.001$); inability to follow two commands and abnormal language ($P < 0.001$); abnormal visual fields ($P < 0.001$); horizontal gaze for gaze palsy ($P = 0.003$); and arm drift, leg drift, and a facial palsy ($P < 0.001$). The neurologic examination required 7 minutes to perform.

Of the 96 patients who had none of the listed historical risk factors or neurologic abnormalities, 93 had a normal CT scan, and only 3 had an abnormal scan. Of those 3 patients, only 1 had evidence of increased mass effect; that patient underwent lumbar puncture without complications. The probability of a normal CT scan if the history and physical examination findings were normal was 97%.

In conclusion, when bacterial meningitis is suspected, historical facts and a thorough neurologic examination can identify patients not likely to have an abnormal CT scan. If this guideline can be validated, applying it to practice could reduce the number of CT scans obtained and expedite the performance of diagnostic lumbar puncture in the emergency department.

Intravenous Amphotericin Drip Reduces Side Effects, Nephrotoxicity, and Mortality Compared with Rapid Infusion

Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. BMJ. 2001;322:579-82. [PMID: 11238151]

Liposomal formulations of amphotericin are less toxic than the conventional deoxycholate compound (2); they cause fewer cases of nephrotoxicity and adverse effects. In this study, Eriksson and colleagues postulated that slowing delivery of the conventional formulation by prolonging the duration of infusion might reduce toxicity.

This randomized, controlled trial of 80 consecutive patients compared two rates of infusing amphotericin B deoxycholate (4 hours [rapid] and 24 hours). The investigators measured creatinine clearance, mortality, and infusion-related adverse effects, such as chills, rigors, and vomiting. To be considered for the trial, clinical suspicion of fungal infection, but not proven infection, was required. Most patients had neutropenia, hematologic disorders, and refractory fever and were classified as having possible, probable, or definite fungal infection. Physicians were prevented from treating side effects on the first day of treatment. Patients who had recently received amphotericin B or had a serum creatinine level greater than 300 μmol/L (3.4 mg/dL) were excluded. The cohorts did not differ significantly in age, concurrent treatment, diagnosis, or severity of infectious signs. Creatinine clearance, electrolyte levels, and mortality rates were tabulated.

More patients in the rapid infusion group than in the continuous infusion group experienced side effects: About three times as many had chills or rigors, and twice as many had vomiting. Patients receiving rapid infusion also required significantly more medication to treat adverse effects and had more dose reductions or interruptions; these outcomes could imply that the drug levels were being altered more frequently or that less drug was being given. Creatinine clearance as a percentage of baseline was lower in the rapid infusion group than in the continuous infusion group at the end of the trial: 65% versus 86% ($P = 0.001$), with a median difference of 19% (CI, 9% to 29%). The mortality rates in the two groups differed significantly. Twelve patients in the rapid infusion group died compared with 4 in the continuous infusion group (relative risk, 3.0 [CI, 1.1 to 8.5]; $P = 0.048$). The number needed to treat for benefit with continuous infusion to prevent one death from the use of rapid infusion was 5. There was no significant difference in the electrolyte disturbances caused by the two methods of administering the drug.

Amphotericin infused over 24 hours reduced side effects, nephrotoxicity, and mortality rates. If patients do not have a contraindication to amphotericin deoxycholate and continuous administration is feasible, the drug should be delivered over 24 hours rather than 4 hours.

Cardiology

Earlier Initiation of Lipid-Lowering Therapy Improves Outcomes

Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285:1711-8. [PMID: 11277825]

The long-term benefits of statin drugs on cholesterol level are well established. Emerging research has also suggested that the drugs have additional activities, such as inhibition of platelet aggregation and anti-inflammatory effects, that may prevent endothelial plaque formation. In this global study, funded by Pfizer Inc. and involving 122 centers, Schwartz and colleagues considered whether early initiation of lipid-lowering therapy before hospital discharge improved cardiac outcomes.

A prospective study in Sweden published in 2001 (3) found that among patients with acute myocardial infarction, initiation of lipid-lowering therapy before hospital discharge decreased 1-year mortality rates by 25%. However, this was a cohort study with inherent weaknesses. Another trial (4) examined lipid-lowering medicines given after catheter-based revascularization. Schwartz and colleagues' study is the first randomized trial investigating the benefit in patients with acute coronary syndromes who did not have an intervention.

In this randomized, controlled, double-blind trial, atorvastatin, 80 mg/d, or placebo was given to patients with non–Q-wave myocardial infarction or unstable angina. All patients were 18 years of age or older; had developed a new pattern of chest pain of at least 15 minutes' duration in the previous 24 hours; had electrocardiographic changes in two contiguous leads or wall-motion abnormalities on echocardiography; had new and reversible defects on nuclear studies; or, in the case of a non–Q-wave myocardial infarction, a doubling of the troponin level. Patients with very high lipid levels were excluded because the authors preferred to focus on a composite outcome of cardiac end points rather than lipid levels. In addition, patients with a recent coronary artery bypass graft or Q-wave myocardial infarction within 4 weeks before the study were excluded. The researchers also excluded patients who were likely to receive prompt revascularization, along with those presenting with heart failure, severe anemia, a history of hemodialysis, high liver function test results, diabetes, pregnancy, or lactation.

Atorvastatin or placebo was started within 1 to 4 days after hospitalization. Patients were assessed at 2, 6, and 16 weeks. Treating physicians decided whether to order additional diagnostic and therapeutic measures, but lipids could not be measured during the hospitalization. The primary outcome measure was a composite end point including death, nonfatal myocardial infarction, resuscitated cardiac arrest, and recurrent ischemia. Additional secondary end points were stroke and heart failure.

Over 28 months, 3086 patients were enrolled; 1538 received atorvastatin and 1548 received placebo. Eighty-six percent of the atorvastatin recipients and 88% of the placebo recipients adhered to the prescribed schedule. Baseline characteristics and use of β-blockers, angiotensin-converting enzyme inhibitors, or aspirin did not significantly differ between groups.

The incidence of the composite end point was significantly lower in the atorvastatin group than in the placebo group: 14.8% vs. 17.4% (relative risk, 0.84 [CI, 0.70 to 1.00]; $P > 0.2$). In addition, the atorvastatin recipients had a lower risk for recurrent ischemia that required hospitalization (relative risk, 0.74 [CI, 0.57 to 0.95]; $P = 0.02$), and recurrent ischemia contributed significantly to the differences seen in the primary end point. No significant differences were noted in death, myocardial infarction, or cardiac arrest, but the study was not powered to detect differences in these variables between the groups.

The mean low-density lipoprotein cholesterol level at the beginning of the trial was 3.21 mmol/L (124 mg/dL) in both groups. The mean triglyceride level was 2.03

Table 2. **Clinical Risk Factors for Perioperative Cardiac Death or Myocardial Infarction***

Clinical Risk Factor	Univariate Analysis		Multivariate Analysis			
	OR (95% CI)	*P* Value	OR with Clinical Characteristics Only (95% CI)	*P* Value	OR with Clinical Characteristics and DSE Results (95% CI)	*P* Value
History of congestive heart failure	5.7 (2.7–12.1)	<0.001	3.0 (1.3–6.9)	0.009	2.3 (0.9–5.5)	0.08
Previous myocardial infarction	3.6 (1.9–6.8)	<0.001	2.5 (1.2–5.3)	0.01		
History of stroke	4.1 (2.0–8.1)	<0.001	3.4 (1.6–7.3)	0.001	3.2 (1.4–731)	0.001
Current stable or previous angina	3.3 (1.8–6.0)	<0.001	2.1 (1.1–4.3)	0.03		
Age ≥ 70 years	2.0 (1.1–3.7)	0.02	1.9 (1.0–3.6)	0.05	1.9 (1.0–4.0)	0.07
Perioperative β-blocker therapy			0.3 (0.1–0.7)	0.009	0.1 (0.0–0.3)	0.001
DSE showing 1–4 new RWMA					13.9 (6.1–31.7)	0.001
DSE showing ≥5 new RWMA					16.7 (6.0–47.0)	0.001

* DSE = dobutamine stress echocardiography; OR = odds ratio; RWMA = regional wall-motion abnormalities.

mmol/L (180 mg/dL), and the mean high-density lipoprotein cholesterol level was 1.19 mmol/L (46 mg/dL). After 6 weeks of treatment, the low-density lipoprotein cholesterol levels decreased by 40% (mean, 1.86 mmol/L [72 mg/dL]) in the atorvastatin group and increased by 12% (mean, 3.49 mmol/L [135 mg/dL]) in the placebo group. The high-density lipoprotein cholesterol level was unchanged. Triglyceride levels decreased by 16% in the atorvastatin group (mean, 1.57 mmol/L [139 mg/dL]) and increased by 9% in the placebo group (mean, 2.11 mmol/L [187 mg/dL]). The frequency of abnormal liver function test results was 2.5% greater in the treatment group. Liver enzyme levels normalized after discontinuation of atorvastatin therapy, and no patients developed myositis.

This study suggests that atorvastatin administered soon after admission for an acute coronary syndrome may be beneficial. The study did not define the optimum point at which to start statin therapy. This evidence suggests that before patients with acute coronary syndrome are discharged from the hospital, it is prudent to prescribe a lipid-lowering statin along with initiation of a β-blocker, aspirin, or angiotensin-converting enzyme inhibitor when appropriate.

Perioperative Medicine

Prediction of Postoperative Adverse Cardiac Event Improved with Combination of Clinical History and Preoperative Dobutamine Stress Echocardiography Results

Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA. 2001; 285:1865-73. [PMID: 11308400]

In this global multicenter cohort study, Boersma and colleagues examined the role of medical history, preoperative dobutamine stress echocardiography results, and the use of β-blocker therapy in the incidence of cardiac events in 1351 consecutive patients undergoing major vascular surgery. The primary end points were nonfatal myocardial infarction and cardiac death within 1 month of surgery. A total of 1091 patients (87%) underwent dobutamine stress echocardiography according to protocol because they had at least one of the following clinical risk factors for adverse cardiac events: age older than 70 years; history of angina, myocardial infarction, or congestive heart failure; treatment for ventricular arrhythmia or diabetes mellitus; or limited exercise capacity. An additional 245 patients had dobutamine stress echocardiography ordered at the discretion of their physician. Of the 360 patients who had perioperative β-blocker therapy, 301 were receiving long-term therapy and 59 were randomly assigned to receive this therapy according to the protocol of the Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography (DECREASE) study (5). The patients receiving β-blocker therapy had a slightly worse risk profile, with a higher prevalence of history of myocardial infarction and unstable angina.

The authors performed both univariate and multivariate analyses to evaluate the relationship between adverse cardiac outcomes (cardiac death or myocardial infarction) and clinical characteristics, dobutamine stress echocardiography results, and perioperative β-blocker therapy.

In the univariate analysis, patients with a history of congestive heart failure, myocardial infarction, or stroke had the highest odds ratio for myocardial infarction or cardiac death (**Table 2**). In the univariate analysis of the preoperative dobutamine stress echocardiography results, patients with several new regional wall-motion abnormalities had the highest odds ratio for a cardiac event. Multivariate analysis that included each of these variables showed that new regional wall-motion abnormalities on dobutamine stress echocardiography, a history of stroke, and congestive heart failure independently predicted adverse cardiac outcomes.

On the basis of these study results, the authors developed a risk classification model. Patients were stratified for risk by the composite end points of Lee and colleagues' revised cardiac index (6), which gives 1 point each for congestive heart failure; history of myocardial infarction, renal insufficiency, diabetes mellitus, and angina; age older than 70 years; and high-risk surgery. Patients with fewer

Table 3. **Selected Variables from Postoperative Pneumonia Risk Index**

Preoperative Risk Factor	Point Value
Type of surgery	
Abdominal aortic aneurysm repair	15
Thoracic	14
Upper abdominal	10
Neck	8
Neurosurgery	8
Vascular	3
Emergency	3
Age	
≥80 y	17
70–79 y	13
60–69 y	9
50–59 y	4
General health	
Functional status	
Totally dependent	10
Partially dependent	6
Weight loss > 10%	7
Current smoker in last year	3
Alcohol intake > 2 drinks/d in last 2 weeks	2
Medical history	
History of chronic obstructive pulmonary disease	5
Impaired sensorium	4
History of stroke	4
Long-term steroid use	3
General anesthetic	4
Transfusion > 4 units	3

than 2 points had a low risk for cardiac events (<2%) regardless of dobutamine stress echocardiography result. Patients with scores of 3 or more but without new regional wall-motion abnormalities also had a low risk for complication if they took perioperative β-blocker therapy. Those with more than four new wall-motion abnormalities had a relatively high risk for perioperative cardiac complications (>6%) despite receiving β-blocker therapy. Each 1-point increase in Lee and colleagues' revised cardiac index carried an odds ratio of 1.6 (CI, 1.1 to 2.2; $P = 0.01$).

Limitations of the study included its status as a secondary analysis, retrospective patient risk stratification, and failure to treat the classification system in a new group of patients.

The combination of a clinical score based on age and clinical history with preoperative dobutamine stress echocardiography results has practical implications for the preoperative evaluation of patients undergoing vascular surgery. Because patients with 0 points on Lee and colleagues' index had low mortality rates regardless of β-blocker use or preoperative dobutamine stress echocardiography results, neither of these interventions would be necessary for assessing or reducing risk. Patients with any one of the listed risk factors should benefit from perioperative β-blocker therapy, but if the risk index score is less than 3, they would not benefit from dobutamine stress echocardiography. Those who had three or more of the revised cardiac index risk factors may receive the greatest benefit from dobutamine stress echocardiography for further preoperative risk stratification. The study findings suggest that patients with four or more new regional wall-motion abnormalities need to undergo invasive testing and revascularization, if indicated, before surgery.

Preoperative Clinical History Predicted Postoperative Pneumonia

Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med. 2001; 135:847-57. [PMID: 11712875]

This large study from 100 Veterans Affairs medical centers sought to develop and validate a preoperative risk index to predict the incidence of postoperative pneumonia (as per the Centers for Disease Control and Prevention definition of nosocomial pneumonia after surgery). The investigators studied a prospective cohort of 160 805 patients who underwent noncardiac surgery from 1 September 1997 through 31 August 1999 to develop the index and then applied the criteria to a cohort of 155 266 patients from 1 September 1995 to 31 August 1997 to validate the index. The researchers excluded patients who had preoperative pneumonia, were ventilator dependent, or developed nosocomial pneumonia after respiratory failure.

A total of 2466 patients (1.5%) developed postoperative pneumonia. Patients with pneumonia tended to be older (mean age [±SD], 68.9 ± 10.9 years vs. 61.2 ± 13.3 years; $P < 0.001$). Overall mortality after 1 month was significantly higher in patients with postoperative pneumonia (21% vs. 2%; $P < 0.001$). Other serious postoperative complications associated with postoperative pneumonia were sepsis, respiratory failure, cardiac arrest, a prolonged ileus, and myocardial infarction.

Multivariate analysis showed that preoperative serum creatinine level, diabetes, congestive heart failure, ascites, end-stage renal disease, recent chemotherapy, and dyspnea did not predict postoperative pneumonia.

General health and immune status, respiratory status, type of anesthesia, and type of surgery were the important predictors of pneumonia. Abdominal aortic aneurysm re-

Table 4. **Postoperative Pneumonia Risk Index Class and Observed Rate of Pneumonia**

Risk Class (Points)	Rate of Pneumonia, %	
	Development Cohort	Validation Cohort
1 (0–15)	0.24	0.24
2 (16–25)	1.19	1.18
3 (26–40)	4.0	4.6
4 (41–55)	9.4	10.8
5 (>55)	15.8	15.9

pair (odds ratio, 4.29 [CI, 3.34 to 5.50]), thoracic surgery (odds ratio, 3.92 [CI, 3.46 to 4.67]), emergency surgery (odds ratio, 1.33 [CI, 1.16 to 1.54]), and a general anesthetic (odds ratio, 1.56 [CI, 1.36 to 1.80]) carried the highest risk for postoperative pneumonia compared with other surgeries or types of anesthetia. Age older than 80 years (odds ratio, 5.63 [CI, 4.62 to 6.84]), poor functional status (odds ratio, 2.83 [CI, 2.33 to 3.43]), recent weight loss (odds ratio, 1.92 [CI, 1.68 to 2.18]), and alcohol use (odds ratio, 1.24 [CI, 1.08 to 1.42]) were significant predictors.

The authors created a point scoring system to predict postoperative pneumonia, calculated each patient's risk score, and placed each patient into one of five risk levels (**Tables 3** and **4**). The risk index predicted the incidence of postoperative pneumonia in the validation cohort with good discrimination and calibration. The C-statistic was 0.779, and the Hosmer–Lemeshow goodness-of-fit statistic was 0.01 ($P > 0.2$).

In summary, this study determined the patient- and surgery-specific risk factors that increase the likelihood of developing postoperative pneumonia. The key contribution of this research is the validation of a method for predicting an individual patient's risk for pneumonia after noncardiac surgery. The usefulness of this rule in guiding postoperative decision is unknown.

Endocrinology

Intensive Control of Blood Glucose Reduces Mortality Rates in Critically Ill Patients

van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359-67. [PMID: 11794168]

Hyperglycemia has been associated with complications in critically ill patients (7), and glucose control has been identified as a favorable goal in diabetic patients after myocardial infarction (8). These observations motivated researchers at the Catholic University in Belgium to examine intensive insulin therapy in intensive care unit (ICU) patients to determine whether strict control of blood glucose levels would reduce morbidity and mortality.

All participants were mechanically ventilated patients in surgical ICUs. Moribund patients, those who already had do-not-resuscitate orders, and those who were participating in other clinical trials were excluded. A total of 1548 patients were randomly assigned to receive an insulin drip when the glucose level was greater than 6.1 mmol/L (110 mg/dL) ($n = 765$) or greater than 11.9 mmol/L (215 mg/dL) ($n = 783$). The sex distribution, age, and admission diagnoses were similar for both groups.

The intensive insulin regimen yielded significantly lower morning blood glucose levels. In addition, the intensive insulin group had decreased all-cause mortality in the ICU, decreased inpatient all-cause mortality, decreased mortality in the context of bacteremia, and reduced length of stay in the ICU. Mortality in the ICU was 8% in the intensive insulin group and 4.6% in the conventional therapy group ($P < 0.04$); the benefit was greatest in patients with multiorgan failure and sepsis. The estimate for the mortality reduction was 32% (CI, 2% to 55%; $P < 0.04$). Thirty-nine (5%) patients in the treatment group experienced hypoglycemia compared with 0.5% of patients in the conventional group. The number needed to treat for harm in 1 patient was 22.

Although these data are compelling, the study had several limitations that hinder its generalizability: It was done in a surgical ICU at only one center and included only mechanically ventilated patients. In addition, the study was not completely blinded. Nevertheless, the authors demonstrate a substantial mortality benefit from intensive insulin therapy. Further studies of this treatment strategy are needed in critically ill medical patients.

Critical Care

Activated Protein C Reduces Mortality in Patients with Severe Sepsis

Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699-709. [PMID: 11236773]

For many years, critical care researchers have been studying ways to intervene successfully with the cascade of events seen in the systemic inflammatory response of ICU patients or to modulate the mediators of this response. This global trial involving 164 centers sought to determine whether treatment with activated protein C (with its antithrombotic, fibrinolytic, and anti-inflammatory properties) decreases all-cause mortality in patients with severe sepsis. The study sample consisted of patients with systemic inflammation and organ failure due to acute infection. The authors excluded HIV-infected patients, transplant recipients, patients undergoing hemodialysis, and patients with liver disease.

A total of 1778 patients were enrolled in a randomized, double-blinded, placebo-controlled trial. The primary end point was 28-day mortality. After per-protocol exclusions, 1690 patients received either the study drug or placebo. The study group ($n = 850$) received activated protein C, and the controls ($n = 840$) received a placebo infusion. The two groups had similar proportions of men and women, Acute Physiology and Chronic Health Evaluation (APACHE) scores, and degree of organ dysfunction. The 28-day mortality rate was 24.7% (210 of 850) in the activated protein C group compared with 30.8% (259 of

840) in the placebo group ($P = 0.005$). Relative risk reduction was 19.4% (CI, 6.6% to 30.5%); the absolute risk reduction was 6.1%. The number needed to treat for benefit to prevent one death was 16.

Because activated protein C is fibrinolytic and inhibits thrombin formation, the most common side effect was severe bleeding: 3.5% in the activated protein C group and 2.2% in the control group ($P = 0.06$). Study drug therapy was stopped 1 hour before any invasive procedures, but severe bleeding still occurred in some patients. The number needed to treat for harm in 1 patient was 66. The study was stopped after the second interim analysis because of the statistically significant reduction in mortality rates in the treated patients.

Although activated protein C did improve outcomes, the drug is very expensive and its cost-effectiveness is unknown. Because enrollment stopped after the interim analysis, there were too few adverse events to rule out a clinically important increase in adverse events in patients assigned to activated protein C. The increased rate of adverse events in the activated protein C group was not statistically significant ($P = 0.08$).

Despite these concerns, the decrease in mortality is noteworthy. Activated protein C may be the first major advance in the treatment of sepsis to emerge in some time. It is currently unclear which patients would benefit the most from the therapy, and more trials are needed to determine rates of complications and how to limit them.

Early, Intensive Resuscitation of Critically Ill Patients in Emergency Department Improves Outcome

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77. [PMID: 11794169]

Rivers and colleagues evaluated the role of early ICU-level care given to critically ill patients *before* admission to the ICU. The study focused on patients with systemic inflammation and organ failure due to acute infection. All patients had at least two of four criteria for the systemic inflammatory response criteria and had a systolic blood pressure lower than 90 mm Hg or a blood lactate level greater than 4 mmol/L.

After applying many exclusion criteria, the authors randomly assigned the patients to one of two levels of pre-ICU care. The early goal-directed therapy group consisted of 130 patients, and the standard treatment group contained 133 patients. The primary end points were mortality, APACHE II scores, hemodynamic measurements, and key laboratory indices, including lactate and blood gas levels. In the early goal-directed therapy group, 6 hours of treatment was initiated in the emergency department with advice from a critical care consultant. According to protocol, a central venous catheter and an arterial line were placed, and hemodynamic monitoring was initiated in the emergency department. Antibiotic therapy was started at the discretion of the physician. Patients received volume resuscitation to achieve a central venous pressure of 8 to 12 mm Hg. Vasoactive agents were added to maintain mean arterial pressure at 65 to 90 mm Hg. If central venous oxygen saturations were less than 70%, patients received blood transfusion until the hematocrit was greater than 0.30. If central venous oxygen saturation remained less than 70%, inotropic agents were added. After meeting these standards, the patients were transferred to the ICU. Patients in the control group received standard care per the study institution.

The baseline characteristics of the two groups (sex, age, and time until initiation of therapy) and the distribution of the types of shock were similar. Antibiotic treatment was not significantly different between the groups.

The inpatient mortality rate was lower in the early intervention group than in the standard treatment group: 30.5% versus 46.5% ($P = 0.009$). Over the first 72 hours, aggressively treated patients also had lower lactate levels, higher pH, higher oxygen saturation, and lower APACHE II scores. Mortality at 28 days was 33% in the early intervention group and 49% in the standard treatment group ($P = 0.01$). The relative risk for death was 0.58 (CI, 0.39 to 0.87; $P = 0.01$).

This study emphasizes the importance of assessing and stabilizing patients as early as possible. The model of care could be applied widely if critical care and emergency department physicians work together closely in an emergency department with adequate nursing care and other resources.

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AD LIBITUM

The Knowledge

> Man comes not from an egg but from
> an animalcule in the masculine seed
> –Antoni van Leewuenhoek, 1683

And now that it was done,
Should he announce what had been seen?
He had taken care not to defile himself
And on his awakening
Had let a little drop fall
Onto the reticule of his microscope.
There, the twisting, squirming worms
Were verily the same as he had seen
In the sexual emissions of the beasts—
His dog, the cow, a goat
Now he himself.
Again and again he asked their origin.
Was this Discovery a part of the Divine plan,
Or some Forbidden knowledge of the Adversary?
At times he believed
A little man, fully formed, rested
Within the head of a microscopic worm.
But then the image gone,
Was it his own fantasy?
He planned to write the Royal Society,
Had sent other Correspondences
Of both empiric and theoretic nature.
Yet he was not blind to the risks,
Knew of the Dialogue of the Two World Systems,
Its consequences—
Galileo on his knees, recanting;
Then house arrest for life.
Men had been burned before for their thoughts,
And Delft was alive with spies.

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PERSPECTIVE

Prevention of Plaque Rupture: A New Paradigm of Therapy

James S. Forrester, MD

Acute coronary syndromes—unstable angina, myocardial infarction, and sudden cardiac death—are caused by acute disruption of an unstable coronary atheroma. Unstable plaques have three histologic characteristics: a large lipid core, many inflammatory cells, and a thin fibrous cap. Because the unstable plaque is not necessarily obstructive, it may cause no symptoms before rupture. The cellular processes that lead to the characteristic histologic features of unstable plaque have recently been identified. This new understanding of the cell biology of plaque instability suggests new therapeutic strategies: passivation of the endothelium, reduction of low-density lipoprotein (LDL) in the vessel wall by decreasing serum LDL levels or accelerating reverse cholesterol transport, inhibition of LDL oxidation, inhibition of inflammatory cytokine expression, and inhibition of thrombus formation. Although the morbidity and mortality resulting from acute coronary disease have been reduced by more than 50% over the past 30 years, it is reasonable to anticipate further reductions of similar magnitude in the decade ahead.

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For author affiliation, see end of text.

Clinical strategies for preventing acute coronary syndromes now focus on preventing plaque instability. The concept has evolved over several decades. Beginning in the 1980s, angioscopy revealed atheroma with a smooth surface in patients with stable angina but showed atheroma with a disrupted intimal surface in patients with acute coronary syndromes (**Figure 1**) (1). Pathologists subsequently demonstrated that disrupted lesions have three characteristic histologic features: a large lipid core, an abundance of inflammatory cells, and a thin fibrous cap (2, 3). Angiographers found that these unstable lesions are not necessarily severely stenotic (4). Finally, in the middle and late 1990s, plaque instability was even more clearly defined when cytokines and enzymes that cause plaque instability at the level of cytokines were identified (**Figure 2**). In this article, I describe the steps in plaque destabilization and link them to a set of clinical strategies that can be expected to substantially decrease the incidence of acute coronary syndromes.

MECHANISMS RESPONSIBLE FOR EVOLUTION OF UNSTABLE PLAQUE

Endothelial Activation

The process of plaque destabilization begins with endothelial activation (**Figure 3**). Some of the endothelial cell activators are the familiar traditional risk factors (increased cholesterol levels, hypertension, and smoking), whereas others (for example, homocysteinemia, immune complexes, and other infectious agents) have been identified more recently (5, 6). The level of endothelial cell activation can change very rapidly (7, 8). For instance, Mellwig and colleagues (8) found a 30% increase in stress-induced coronary blood flow 20 hours after low-density lipoprotein (LDL) apheresis, which lowered mean LDL levels from 194 to 81 mg/dL (5.0 to 2.0 mmol/L), and Vogel (6) found substantial reduction in forearm vascular reactivity in a 4-hour period after a fatty meal. The activated endothelial cell expresses cell adhesion molecules, which cause circulating blood cells to adhere to the endothelium and enter the blood vessel wall. Animals deficient in adhesion molecules have 40% smaller lesions than those with normal production (9). Adhesion molecules are found on the surface of human atheroma (10) and are strongly associated with increased intimal leukocyte accumulation. Serum levels of adhesion molecules correlate directly with carotid intimal thickness (11).

Formation of the Lipid Core

As cells enter the vessel wall, cholesterol also enters as LDL. Macrophages avidly take up cholesterol from apolipoprotein B–containing lipoproteins and are trapped in the subendothelial space, forming the lipid core. The anatomic differences between stable and disrupted plaques are striking. In aortae with disrupted plaque, unstable lesions have a much greater cross-sectional area occupied by lipid (64% vs. 14%), an eightfold greater area occupied by macrophages, and a thinner fibrous cap (0.13 mm vs. 0.44 mm) (12).

Reverse Cholesterol Transport

Cholesterol in the blood vessel wall is transferred to high-density lipoprotein (HDL) (13–15) for transport back to the liver for excretion in the bile. Reverse cholesterol transport involves cholesterol transfer from cell membranes to phospholipid acceptor particles, the most important of which are nascent HDL particles and two proteins. Cholesterol in the nascent HDL is esterified by lecithin cholesterol acyltransferase to cholesterol esters, and cholesteryl ester transfer protein exchanges the ester for triglyceride. Because HDL also inhibits adhesion molecule expression (16), is an antioxidant (17), and blocks matrix metalloproteinase expression, the antiatherogenic mechanisms through which HDL act are not firmly established.

LDL Oxidation

The native LDL that enters the blood vessel wall undergoes oxidation by oxygen free radicals (18). The uptake of oxidized LDL by macrophages stimulates expression of cytokines and proteolytic enzymes. In humans, antibodies against LDL are found in atherosclerotic lesions, and plasma contains antibodies that react with oxidized LDL

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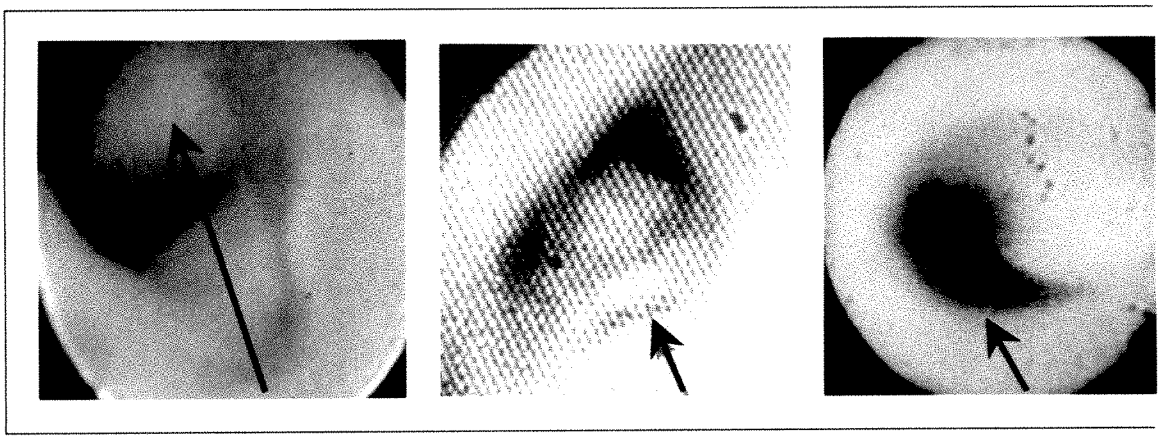
Figure 1. **The angioscopic appearance of stable and unstable atheroma.**



Left. The typical smooth surface of a stable atheroma in a patient with stable angina. **Middle.** The disrupted intimal surface of an atheroma in a patient with unstable angina. **Right.** A thrombus on the surface of a disrupted atheroma in a patient with acute myocardial infarction.

(19). Furthermore, the level of plasma-oxidized LDL increases with age and is substantially higher in patients with atherosclerosis than in controls (20).

Cell Activation in the Vessel Wall

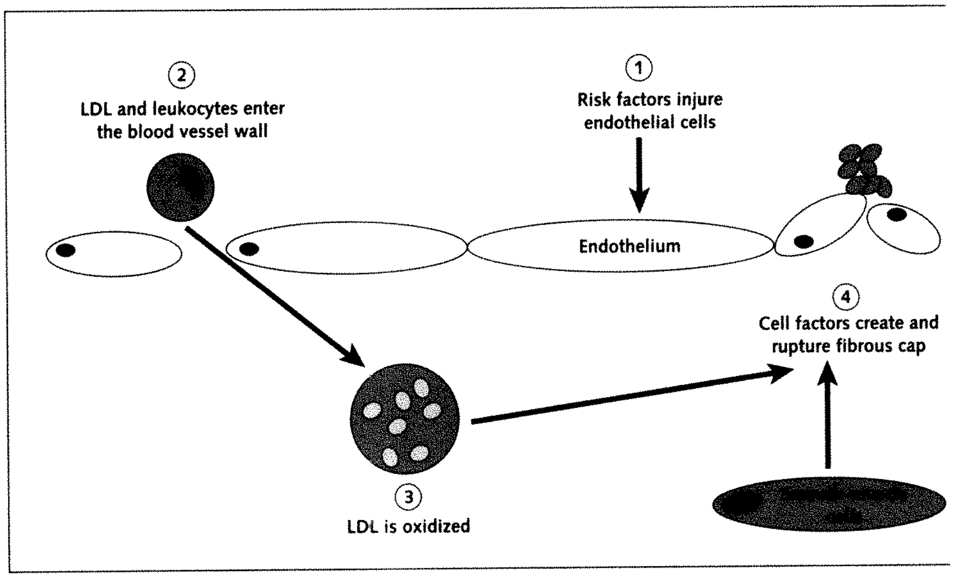
In an unstable plaque, every cell type is activated. This process is strikingly similar to that of other chronic inflammatory conditions, such as rheumatoid arthritis (21). The smooth-muscle cell changes its phenotype, developing twice the volume of secretory granules as the normal quiescent cell (22). The blood monocyte becomes a tissue macrophage (23). The mast cell becomes positive for tumor necrosis factor-α, and the percentage of mast cells that are degranulated increases 15- to 20-fold (24, 25). The T lymphocyte is also activated (26).

A spectrum of cytokines with many overlapping actions determine whether the individual atheroma progresses to stability or to instability (27–30). For instance, tumor necrosis factor-α activates endothelial cells, transforming growth factor-β stimulates the production of lipoprotein-trapping proteoglycans, colony-stimulating factors cause macrophage replication, and interferon-γ suppresses smooth-muscle replication (26, 31).

Thinning and Rupture of the Fibrous Cap

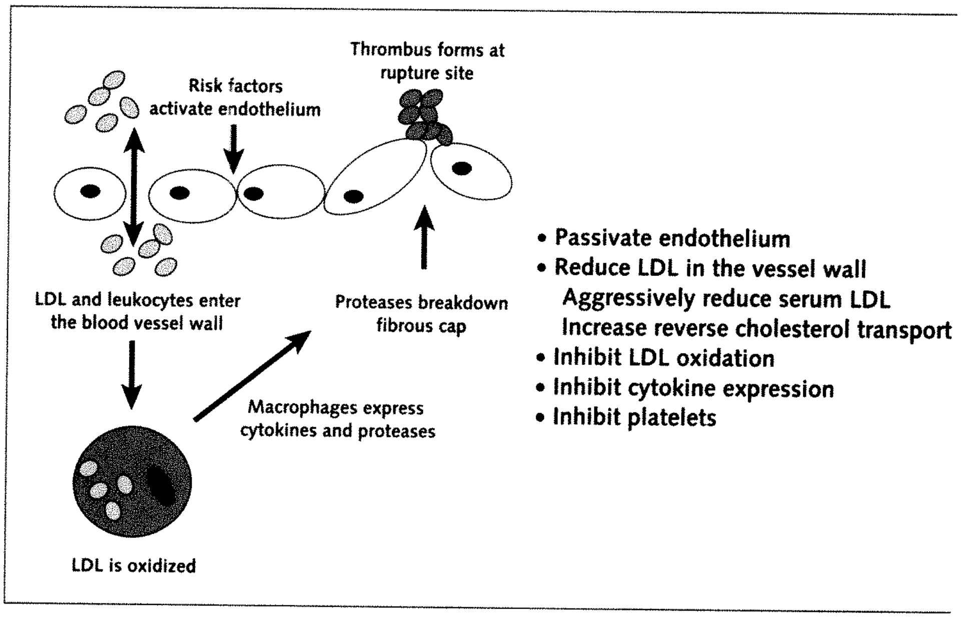
Smooth-muscle cells produce collagen and other extracellular matrix proteins, which provide mechanical strength, whereas activated inflammatory cells, particularly macrophages and mast cells, express enzymes that degrade the collagen (32, 33). In unstable plaque, the balance

Figure 2. **The steps in atheroma destabilization.**


②
LDL and leukocytes enter the blood vessel wall
①
Risk factors injure endothelial cells
Endothelium
④
Cell factors create and rupture fibrous cap
③
LDL is oxidized

Activated endothelial cells express adhesion molecules, which attract leukocytes that enter the blood vessel wall. Low-density lipoprotein (*LDL*) in the vessel wall is oxidized and taken up by macrophages. The activated cells in the vessel wall express cytokines, which maintain the inflammatory process. Proteases digest the fibrous cap, and smooth-muscle cells undergo apoptosis, leading to rupture of the fibrous cap.

Figure 3. **The biological processes that induce plaque destabilization and the therapeutic strategies that inhibit these processes.**


Thrombus forms at rupture site
Risk factors activate endothelium
LDL and leukocytes enter the blood vessel wall
Proteases breakdown fibrous cap
Macrophages express cytokines and proteases
LDL is oxidized
• Passivate endothelium
• Reduce LDL in the vessel wall
Aggressively reduce serum LDL
Increase reverse cholesterol transport
• Inhibit LDL oxidation
• Inhibit cytokine expression
• Inhibit platelets

If the processes are relatively independent, the therapies may have an additive effect. LDL = low-density lipoprotein.

among these competing factors favors collagen breakdown rather than synthesis.

Thinning of the fibrous cap involves at least two processes: increased collagen breakdown by proteases and decreased collagen synthesis by smooth-muscle cells. The family of metalloproteinases, expressed by macrophages, erodes the fibrous cap (34). The expression of metalloproteinases is driven by cytokines, such as tumor necrosis factor-α and interleukin-1, which upregulate macrophage metalloproteinase activity (35–37). Oxidized LDL doubles metalloproteinase expression, whereas native LDL has no effect (38, 39). In addition, collagen synthesis is diminished as a result of both decreased function and apoptosis of the smooth-muscle cell (40, 41). The decrease in the smooth-muscle cell population in unstable plaques reflects increased expression of cytokines, such as tumor necrosis factor-α and interferon-γ, which induce apoptosis.

Remarkably, the extracellular matrix itself helps destroy the fibrous cap. Wallner and colleagues found that the extracellular protein tenascin-C, which induces metalloproteinase expression and causes smooth-muscle cell apoptosis, is not present in the normal vessel wall but is strongly expressed in unstable plaque (42, 43).

Unstable plaques most commonly rupture at the plaque shoulder, where T lymphocytes and macrophages predominate and smooth-muscle cells are less common. Tissue factor content is increased twofold in unstable plaques, which promotes thrombosis when the plaque ruptures (44). **Table 1** summarizes the best-studied cytokines and their effects.

The Contribution of Systemic Inflammation to Local Plaque Instability

An accumulating body of recent evidence suggests that systemic factors may influence local plaque instability. Compared with stable angina, the temperature of culprit lesions is 0.6 °C higher in unstable angina and 1.0 °C higher in myocardial infarction. The plaque's temperature correlates with its macrophage density. Local plaque temperature also correlates with the systemic level of circulating cell adhesion molecules, cytokines, and plasma C-reactive protein (45, 46). These data suggest an interaction

Table 1. **Destabilizing Effects of Cell Products Identified in Unstable Atheroma***

Cell Product (Reference)	Important Action in Unstable Plaque	Other Actions
Tumor necrosis factor-α (36)	Upregulates adhesion molecules	Increases thrombogenicity
Interleukin-1β (36)	Activates endothelial cells	Causes smooth-muscle cell apoptosis
Matrix metalloproteinase (29)	Digests collagen	Digests elastin
Tenascin (42)	Stimulates matrix metalloproteinase expression	Causes smooth-muscle cell apoptosis
Transforming growth factor-β (31)	Stimulates collagen synthesis	Stimulates lipid-trapping proteoglycans
Tissue factor (44)	Promotes thrombin generation	Promotes matrix metalloproteinase expression
Insulin-like growth factor-δ (41)	Suppresses collagen expression	Causes smooth-muscle cell apoptosis

* Each cell product in unstable plaque has multiple actions that contribute to stabilization. In addition, there is substantial overlap among the effects of cytokines. Because of this redundancy, it is unlikely that targeting a single cytokine will be an effective approach.

Table 2. **Key Points***

Unstable plaques cause acute coronary syndromes.
Local inflammation causes plaque instability.
Systemic inflammation augments local inflammation.
Plaque destabilization proceeds through five steps: endothelial activation, LDL entry into blood vessel walls, LDL oxidation, breakdown of the fibrous cap, and thrombus formation.
Each step of plaque destabilization can be inhibited by preventive therapies.
The incidence of acute coronary syndromes can be substantially reduced.

*LDL = low-density lipoprotein.

between systemic and local inflammatory processes. Danesh (47) performed a meta-analysis of seven studies involving 1053 cases of nonfatal myocardial infarction or death related to coronary heart disease; the mean follow-up in these studies was 6 years. The risk ratio of coronary heart disease for persons in the upper tertile of plasma C-reactive protein compared with those in the bottom tertile was 1.7 (47). Similar relationships have been found for other markers of systemic inflammation, such as fibrinogen and amyloid A. It is as yet unclear whether these indicators of systemic inflammation are a marker or a mediator of local plaque instability.

THE BIOLOGICAL BASIS OF UNSTABLE PLAQUE HISTOLOGY

Returning to the three histologic characteristics of unstable plaque, the pathogenesis of each feature can now be defined. The large lipid core results from the entry of lipids and monocytes into the blood vessel wall, a process initiated and maintained by endothelial cell activation. The monocytes are transformed into tissue macrophages by ingestion of oxidized LDL, creating the lipid core. The abundance of inflammatory cells in the unstable plaque results from their attraction to the vessel wall by adhesion molecules and is maintained and promoted by subsequent cytokine-induced cell activation. The thin fibrous cap results from extracellular matrix breakdown that is driven by protease expression induced by both the activated cells and the extracellular matrix. Diminished collagen synthesis as a result of smooth-muscle cell apoptosis occurs concurrently.

From this detailed description of the cell biology of plaque destabilization, it is now possible to extract several broad generalizations (**Table 2**). The fundamental cause of plaque instability is the imbalance of activation and passivation of the cells of the blood vessel wall, that is, inflammation. The final common pathway is the predominance of collagen breakdown over collagen synthesis in the fibrous cap. And, quite unexpectedly, the extracellular matrix is both a target and a modulator in plaque destabilization.

THERAPEUTIC STRATEGIES DERIVED FROM CELL BIOLOGY

The cell biology of plaque destabilization suggests that many routes, other than lowering LDL levels, may provide stabilization. Both epidemiologic data and recent clinical trials support this possibility. Data collected prospectively over 25 years on the relationship between serum cholesterol level and cardiac death in different countries show that within each quartile of serum cholesterol level, cardiac mortality differs as much as fourfold (48). Although this difference in major adverse cardiac events at the same cholesterol level may reflect variations in diet, lifestyle, environment, or genetics, its magnitude indicates the importance of factors beyond blood cholesterol. Reductions in cardiac events without lowering cholesterol levels support this idea.

Within the limited scope of this article and with the understanding that therapies often affect several mechanisms, the biology of plaque instability suggests at least five new strategies (**Figure 3**): passivation of the endothelium, reduction of LDL in the vessel wall by aggressively reducing serum LDL levels or accelerating reverse cholesterol transport, inhibition of LDL oxidation, inhibition of inflammatory cytokine and protease expression, and inhibition of platelets.

Suppression of Endothelial Activation: The Role of Angiotensin Inhibition and Fish Oil

Endothelial activation can be viewed somewhat simplistically as the result of the balance between two of the most important factors that affect endothelial function—angiotensin II and nitric oxide. When the balance is shifted toward angiotensin II, endothelial activation results, with the potential to initiate plaque destabilization. Angiotensin alters the blood vessel wall through many biological mechanisms, only one of which is endothelial activation and promotion of adhesion molecule expression (49). For instance, angiotensin also promotes formation of oxygen free radicals (50) and regulates extracellular matrix function.

Angiotensin-converting enzyme (ACE) inhibitors reduce atherosclerosis in many nonhypertensive animal models, including primates (51). Although the mechanisms for the antiatherosclerotic effect are undefined and probably multiple, ACE inhibitors do reduce adhesion molecule expression and macrophage infiltration in the rabbit model of early accelerated atherosclerosis (52). In Cynomolgus monkeys, Song and colleagues (53) reported that the area of aortic atherosclerosis decreased from 58% to 24% with ACE inhibition; this finding was accompanied by a marked decrease in angiotensin I and II receptor density to normal levels. A similar magnitude of reduction in atherosclerosis has been confirmed with other ACE inhibitors (54). The first randomized, placebo-controlled trial to demonstrate reduction of major adverse cardiac events in normotensive humans is the Heart Outcomes Prevention Evaluation study (55). Ramipril (10 mg orally) or placebo was given for 5 years to 9297 patients without heart failure who were at high risk for a cardiac event (>54 years of age, vascular disease or diabetes, and one additional risk factor). In the treatment group, the event rate was reduced by 22%, suggesting that angiotensin II inhibition has potent antiatherogenic effects. Several ongoing trials seek to confirm the hypothesis. In one of these trials, 14 000 patients with coronary heart disease who have normal left ventricular function are being treated with trandolapril (4 mg/d) added to standard therapy over 5 years; the primary end point is cardiovascular mortality and myocardial infarction.

Angiotensin receptor blockers reduce the development of atherosclerosis in hypercholesterolemic primates. The results of clinical trials have not yet been reported. However, in a study by Navalker and colleagues, patients with normotensive stable coronary disease who were treated with irbesartan (70 to 150 mg/d for 24 weeks) had a decrease in soluble adhesion molecule (36%), tumor necrosis factor-α (54%), and superoxide levels (52%). Because irbesartan did not alter blood pressure in these normotensive patients, the results suggest that the drug independently retarded the inflammatory component of atherosclerosis (56).

Marine n-3 polyunsaturated fatty acids decrease very-low-density lipoprotein (VLDL) and triglyceride levels and elevate HDL levels. In addition, fish oils have modest antihypertensive, antithrombotic, and antiarrhythmic activity (57). Most epidemiologic studies have not shown a relationship between fish intake and a reduction in the prevalence of coronary heart disease. Nonetheless, randomized trials have demonstrated positive effects from administering fish oil after infarction. Both the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione trial (58) and the Diet and Reinfarction Trial (59) observed 10% to 15% reductions in major adverse cardiac events over a 5-year follow-up period. The advice to eat one or more fish meals weekly is reasonable, particularly if these meals are substitutes for saturated fats in animal meats.

Reduction of LDL Entry: The Role of Statins

Substantial lowering of blood lipid levels leads to plaque stabilization. Aikawa and colleagues found that a 16-month lipid-lowering diet fed to hypercholesterolemic rabbits progressively reduced vascular macrophage content by 20-fold. Metalloproteinase immunoreactivity became almost undetectable (60), and interstitial collagen content increased substantially.

New statin dose formulations that permit routine LDL lowering to less than 80 mg/dL (2 mmol/L) raise the issue of very aggressive LDL lowering (61), particularly because atherosclerosis is rare to absent in animals and humans with total serum cholesterol levels less than 160 mg/dL (<4 mmol/L). On the other hand, in epidemiologic studies, the slope of the relationship between major adverse cardiac events and LDL may have an inflection point close to an LDL level of 100 mg/dL (2.5 mmol/L), which strongly suggests a progressively smaller therapeutic benefit as the LDL level is lowered to less than 100 mg/dL. The data from clinical trials are contradictory, possibly reflecting the multiplicity of factors that influence risk and outcome or different burdens of atherosclerotic disease.

In the Cholesterol and Recurrent Events study, patients with a pretreatment LDL level less than 125 mg/dL (<3.2 mmol/L) had no reduction in major adverse cardiac events with statin therapy (62). A subgroup analysis of the West of Scotland Coronary Prevention study (63) also showed no further reduction in coronary heart disease risk beyond a 24% reduction in LDL levels. In contrast, the Post Coronary Artery Bypass Graft trial, which compared LDL lowering to targets of either 95 mg/dL (2.4 mmol/L) or 135 mg/dL (3.5 mmol/L) (64), reported substantially better angiographic and clinical outcomes in the aggressively treated cohort. This benefit increased as duration of follow-up increased from 5 to 8 years. Subgroup analysis in this trial and several other trials have suggested progressively greater benefit at lower levels of on-treatment LDL.

Several ongoing trials are addressing the issue of aggressive LDL lowering. The Treat to New Targets trial has randomly assigned 10 004 patients with coronary heart disease and LDL levels of 130 to 250 mg/dL (3.3 to 6.4 mmol/L) to either 10 mg or 80 mg of atorvastatin; the end point is death or myocardial infarction at 5-year follow-up. This strategy will allow comparison of on-treatment LDL levels of approximately 70 to 80 mg/dL (1.8 to 2.1 mmol/L) to 90 to 110 mg/dL (2.3 to 2.8 mmol/L). The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial, which is sponsored by the manufacturers of pravastatin, aims to demonstrate that there is no difference in clinical outcomes as LDL levels are lowered beyond those close to the current National Cholesterol Education Program guideline. In contrast, the Reversal of Atherosclerosis with Lipitor trial, sponsored by the manufacturers of atorvastatin, aims to show plaque regression in 600 patients who are using the same drug dosages (80 mg of atorvastatin vs. 40 mg of pravastatin) as those being used in the PROVE IT trial; the end point is a coronary intravascular or angiographic event at 18 months. These studies should contribute substantially to defining the value, if any, of aggressive LDL lowering.

Statins, like ACE inhibitors, have pleiotropic anti-inflammatory effects independent of their perceived primary action (**Table 3**). For instance, statins decrease monocyte adhesion independent of cholesterol lowering (65). Animal studies show that LDL lowering with statins (similar to lowering with diet) reduces plaque macrophage and cholesterol ester content, increases the volume of collagen and smooth-muscle cells, and reduces platelet activation and blood hyperviscosity. In a nonrandomized study of 24 patients undergoing carotid endarterectomy, patients were given either statin therapy for 3 months or no lipid-lowering therapy. Atheroma in patients given statin therapy had 75% less lipid core, 40% less oxidized LDL and metalloproteinase, and twice the amount of collagen (66). Statin therapy also reduces thrombin generation by 40% in patients with hypercholesterolemia (67). These pleiotropic

Table 3. **Pleiotropic Actions of Antiatherosclerotic Therapies***

Therapy	Action					
	Improve Endothelial Function	Decrease Low-Density Lipoprotein Levels	Inhibit Low-Density Lipoprotein Oxidation	Increase Reverse Cholesterol Transport	Reduce Inflammation	Inhibit Thrombosis
Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker	X	–	X	–	X‡	–
Statin	X	X	X	†	X‡	–
Vitamin E	X	–	X	–	X‡	–
Fish oil	–	X	–	†	–	X
Increase in high-density lipoprotein levels	X	–	X	X	X	–
Fibrates	X	–	–	†	–	–
Aspirin	–	–	–	–	X	X
Clopidogrel	–	–	–	–	–	X

* Almost all of the methods for reducing plaque instability have many actions on endothelial function, low-density lipoprotein levels, oxidation, reverse cholesterol transport, inflammation, and thrombosis. Dash = published data are not available, but there is not a good basis for suspecting an effect; X = promotes effect.

† Statins, fish oil, and fibrates can increase high-density lipoprotein levels and might thereby accelerate reverse cholesterol transport.

‡ The anti-inflammatory action may result in part from the antioxidant effect.

effects may explain some of the beneficial effects of long-term statin therapy.

Initiation of aggressive therapy to lower LDL levels during hospitalization in patients with acute coronary syndromes may contribute to early plaque stabilization. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (68), treatment with 80 mg of atorvastatin daily was begun during hospitalization and patients were followed through 16 weeks. The average LDL level declined by 40% to 72 mg/dL (1.9 mmol/L) with atorvastatin, but the placebo group was unchanged (68). Compared with the placebo group, the atorvastatin group had a 16% reduction in the composite primary end point event (14.8% vs. 17.4% [$P = 0.048$]), primarily resulting from reduced re-hospitalization for recurrent symptomatic myocardial ischemia. The atorvastatin group had a slight increase in reversible elevation of liver function test results; there were no cases of myositis. On the basis of these and other confirming studies, most cardiologists favor in-hospital initiation of statin therapy in patients with acute coronary syndromes.

LDL levels can also be reduced by preventing dietary cholesterol absorption. Cholesterol acyltransferase facilitates cholesterol absorption from the intestine and is in part responsible for the formation and accumulation of cholesterol esters in the vessel wall. In hamsters, acyl-coenzyme A cholesterol acyltransferase inhibitors reduced cholesterol fatty streak area by 90% after 8 weeks (69). The effect seems to be synergistic with statins. In cholesterol-fed rabbits, Bocan and colleagues found that doses of atorvastatin and an acyl-coenzyme A cholesterol acyltransferase inhibitor that reduced plasma cholesterol levels by 29% and 39%, respectively, resulted in a 60% reduction when administered concurrently (70). The reduction of plasma cholesterol was paralleled by similar reductions in atheroma mass and macrophage area.

Ezetimibe is a specific inhibitor of the receptor responsible for transfer of cholesterol from intestinal lumen into the intestinal wall. Preliminary studies suggest that ezetimibe when used alone lowers LDL levels by 15% to 20% but when used in combination with statins can reduce LDL levels by 60%.

Acceleration of Reverse LDL Cholesterol Transport: The Role of Apolipoprotein A-I, Fibrates, and Niacin

Laboratory data on animals suggest that raising the serum level of HDL or apolipoprotein A-I has several important antiatherosclerotic effects, the most important of which may be the effect on reverse cholesterol transport. Overexpression of human apolipoprotein A-I reduces the progression of atherosclerosis in mice (71, 72). Repeated injections of both purified apolipoprotein A-I (73) and HDL (74) inhibit the development of atherosclerosis in cholesterol-fed rabbits and in apolipoprotein E–deficient mice with an accelerated form of atherosclerosis (75). Antibodies to cholesterol ester transfer protein have been reported to increase HDL levels by 35% and decrease plaque area by 40% in the hypercholesterolemic rabbit (76). Gene transfer of the apolipoprotein A-I gene to the liver of hypercholesterolemic mice induced a 69% increase in apolipoprotein A-I levels, a 54% increase in HDL levels, and a 70% decrease in aortic lesion area (77, 78). The change in lesion area is accompanied by a substantial decrease in lesion macrophage volume.

No currently available clinical therapy increases HDL levels in a magnitude comparable to the statin effect on LDL lowering. Nonetheless, modest increases in HDL associated with triglyceride lowering, with both niacin and fibrates, reduce cardiac event rate. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial, 1264 of 2531 men with coronary heart disease, an HDL level of 40 mg/dL (1.0 mm/L) or less, and an LDL level of 140 mg/dL (3.6 mmol/L) or less were assigned to receive gemfibrozil (1200 mg/d) for 5 years (79). Triglyceride levels decreased 31%, and HDL levels increased 6%. Although LDL levels did not change, the cardiac event rate decreased by 22%. Thus, therapies that substantially increase HDL levels hold major promise.

Inhibition of the Oxidative State: The Role of Vitamins and Diet

Vitamins have well-established ex vivo antioxidant properties. The principal antioxidants that protect the LDL molecule from oxidation are the lipid-soluble agents α-tocopherol, γ-tocopherol, and β-carotene (80, 81). Ascorbic acid regenerates reduced α-tocopherol after it has been oxidized. Vitamin E supplements inhibit atherogenesis in animals, including primates (82). In the Cambridge Heart Antioxidant Study, administration of vitamin E, 400 to 800 mg daily, to postinfarction patients was associated with a 41% reduction in the subsequent rate of myocardial infarction, although overall mortality was unchanged (83). Two larger randomized trials, however, have failed to demonstrate a beneficial effect of vitamin E. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione trial, 11 324 patients who recently had a myocardial infarction were randomly assigned to receive vitamin E (300 mg/d), n-3 polyunsaturated acid (1 g/d), both, or neither. Although n-3 polyunsaturated fatty acids reduced major adverse cardiac events by 10% to 14% over 3.5 years, vitamin E had no beneficial effect (84). This result was subsequently supported by the Heart Outcomes Protection Evaluation study, in which 8541 high-risk patients were randomly assigned to receive either vitamin E (400 IU/d) or placebo over a 4.5-year period (85). The number of nonfatal myocardial infarctions, strokes, and deaths from cardiovascular causes did not differ. Although less extensively studied, treatment with vitamin A and vitamin C has produced similar negative results (6). Given the central role that oxygen radicals and oxidized LDL play in the pathogenesis of atherosclerosis in the animal model, the failure of antioxidant vitamin supplementation to reduce major adverse cardiac events in humans is largely unexplained.

Another potentially therapeutic vitamin is folic acid because of its effect on homocysteine levels. As many as 20% of patients with coronary heart disease have elevated levels of homocysteine (86). High homocysteine levels predict cardiovascular and noncardiovascular death. In a population-based cohort of 4766 Norwegian men and women (range, 65 to 67 years of age), homocysteine levels of 9 μmol/L were significantly associated with a 50% increase in cardiovascular death (87). Other investigators have demonstrated that vitamin B and folic acid decrease homocysteine levels; however, to date, clinical trials have not demonstrated that lowering homocysteine levels reduces major adverse cardiac events (88).

Although antioxidant vitamins have thus far failed, we know that diets with antioxidant properties substantially reduce major adverse cardiac events after acute myocardial infarction. The three large randomized trials that have examined the effect of diet in patients with coronary heart disease have shown substantial reductions in major adverse cardiac events (89–91). The Lyon Diet Heart study randomly assigned 605 patients who had experienced their first myocardial infarction to a Mediterranean-type or a prudent western diet; the follow-up period was 4 years (89). There were 95 cardiovascular events in the Mediterranean diet group compared with 180 events ($P < 0.001$) in the prudent western diet group. High blood pressure and cholesterol levels were independent and joint predictors of major adverse cardiac events, thus indicating that the Mediterranean diet did not alter the usual relationships between risk factors and major adverse cardiac events. The many differences between the Mediterranean diet and the prudent western diet preclude any attempt to identify a predominant mechanism. Within this limitation, however, a leading candidate for efficacy in the Mediterranean diet is the n-3 class of essential fatty acids—particularly α-linolenic acid (92).

Inhibition of Inflammatory Cytokines: The Role of Antibiotics and Aspirin

An association between *Chlamydia pneumoniae* and atherosclerosis is suggested by seroepidemiologic studies, which show that patients with coronary heart disease frequently have antibodies against *Chlamydia* species (93) and that atheroma frequently contains these species (94). In 1997, a small English study suggested that azithromycin reduced cardiac events in survivors of myocardial infarction (95, 96). Two subsequent randomized clinical trials of antibiotics have failed to reproduce these results (97, 98). In the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia study, 302 patients who were randomly assigned to receive placebo or azithromycin for 3 months and then followed for 2 years had no differences in cardiac events (99). Approximately 3500 patients are needed to show a 20% reduction in event rate; two adequately powered trials of coronary artery disease are under way, with results expected in late 2003 (100, 101).

Compared with controls, patients with unstable angina have more than twice the blood levels of interleukin-6, C-reactive protein, and macrophage colony-stimulating factor (102), and these levels decrease after 6 weeks of aspirin treatment. These data, taken together with data from previous studies demonstrating the efficacy of aspirin in reducing early posthospitalization cardiac events, suggest that the anti-inflammatory effect of aspirin may be additive to its antithrombotic effect in patients with plaque instability.

Inhibition of cytokine expression can be directed at a specific cytokine or, more generally, at the inflammatory process. It is possible to inhibit metalloproteinases in vivo. Tissue inhibitors of metalloproteinases naturally antagonize the action of metalloproteinase (103, 104). George and colleagues (104) overexpressed tissue inhibitor of metalloproteinase-3 at the luminal surface of porcine saphenous veins before carotid artery grafting. Neointima formation was reduced 58%, and metalloproteinase expression was reduced throughout the vessel wall. To date, there are no reported trials of tissue inhibitors of metalloproteinase for preventing plaque instability. Furthermore, the practicality of systemic suppression of metalloproteinases and specific cytokines is problematic because they participate in normal tissue functions.

Inhibition of Thrombosis: The Role of Aspirin and Clopidogrel

Aspirin reduces cardiac events in patients with acute coronary syndromes and in patients not known to have coronary heart disease. The Italian Primary Prevention Project compared low-dose aspirin (100 mg/d) to no therapy in a randomized trial of 4495 persons with one or more cardiovascular risk factors (hypercholesterolemia, diabetes, hypertension, obesity, family history of coronary heart disease, or older age) (105). The trial was terminated at 3.6 years when evidence from two other trials showed benefit in primary prevention. In the Italian study, aspirin reduced the frequency of major adverse cardiac events from 8.2% to 6.3%. Severe bleeding was more frequent in the aspirin group (1.1% vs. 0.3%), and one bleeding complication was fatal in the 8000 person-treatment years. As a result of these findings, cardiologists typically recommend low-dose aspirin for primary prevention of coronary heart disease in persons who have one or more risk factors when blood pressure is not elevated.

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial, 12 562 patients received aspirin alone or aspirin plus clopidogrel (75 mg/d) (106). At 9-month follow-up, the clopidogrel group experienced a 20% reduction in cardiac events; the absolute increase in major bleeding was 1%. These results contrast with the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial, which was conducted in 19 185 patients with a history of recent stroke, myocardial infarction, or symptomatic peripheral artery disease. Over a 1- to 3-year follow-up period, cardiac events were reduced from 5.8% to 5.3%, a relative risk reduction of only 9% (107).

The multiple potential directions for prevention of plaque instability raise important practical questions. One critical question is the increment of benefit, if any, to be obtained from therapies added to diet and LDL lowering. Clinical trials to date provide little insight. One ongoing trial compares the current standard for optimal medical therapy to angioplasty plus optimal medical therapy. The trial is being conducted in 3260 patients with known coronary heart disease who are being followed for 3 years. Optimal medical therapy includes a statin, an ACE inhibitor, aspirin, a β-blocker, and a calcium-channel blocker, as is appropriate for patients with stable angina. For patients with unstable angina, optimal therapy also includes nitrates, a glycoprotein 2B/3A inhibitor, and heparin. The primary end points are death, myocardial infarction, and refractory angina necessitating bypass surgery. Extensive data on cost-effectiveness and quality of life are also being collected.

CONCLUSION

Cell biology has created a new paradigm for prevention of acute coronary syndromes resulting from plaque rupture. The five new therapeutic directions for plaque stabilization are endothelial passivation, reduction of LDL in the vessel wall by very aggressive LDL lowering or acceleration of reverse cholesterol transport, inhibition of LDL oxidation, inhibition of inflammatory cytokine and protease expression, and inhibition of platelets. Each of these pathways can be affected by currently available therapies. If their effects are additive, major further reductions in coronary events will be possible in the future.

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CLINICAL GUIDELINES

Postmenopausal Hormone Replacement Therapy for Primary Prevention of Chronic Conditions: Recommendations and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations for use of hormone replacement therapy for the primary prevention of chronic conditions in postmenopausal women and updates the 1996 USPSTF recommendations on this topic. The complete information on which this statement is based, including evidence tables and references, is available through the USPSTF Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse (www.guideline.gov) The USPSTF reviewed the evidence on the use of postmenopausal hormone replacement therapy and the following outcomes: cardiovascular disease, including CHD and stroke; osteoporosis and fractures; thromboembolism; dementia and cognitive function; breast, colon, ovarian, and endometrial cancer; and cholecystitis. The USPSTF also reviewed evidence of the effects of hormone replacement therapy on phytoestrogens and osteoporosis and cardiovascular disease. The use of hormone replacement therapy for relieving active symptoms of menopause, such as hot flashes, urogenital symptoms, and mood and sleep disturbances, among others, is outside the scope of these USPSTF recommendations, and literature on this topic was not reviewed. Sources for estimates of benefits and harms cited in this Recommendation statement are described in the summary of the evidence available from the Agency for Healthcare Research and Quality.

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*For a list of the members of the U.S. Preventive Services Task Force, see Appendix.

SUMMARY OF RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. This is a **grade D recommendation.** (See **Appendix Table 1** for a description of the USPSTF classification of recommendations.)

The USPSTF found fair to good evidence that the combination of estrogen and progestin has both benefits and harms. (See **Appendix Table 2** for a description of the USPSTF classification of levels of evidence.) *Benefits include increased bone mineral density (good evidence), reduced risk for fracture (fair to good evidence), and reduced risk for colorectal cancer (fair evidence). Harms include increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), coronary heart disease (CHD) (fair to good evidence), stroke (fair evidence), and cholecystitis (fair evidence). Evidence was insufficient to assess the effects of hormone replacement therapy (HRT) on other important outcomes, such as dementia and cognitive function, ovarian cancer, mortality from breast cancer or cardiovascular disease, or all-cause mortality.*

The USPSTF concluded that the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause, such as vasomotor symptoms (hot flashes) or urogenital symptoms. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.

The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. This is a **grade I recommendation.**

The USPSTF found fair to good evidence that the use of unopposed estrogen has both benefits and harms. Although most current data come from observational studies, likely benefits include increased bone mineral density, reduced fracture risk, and reduced risk for colorectal cancer. Likely harms include increased risk for venous thromboembolism, cholecystitis, and stroke; in women who have not had a hysterectomy, unopposed estrogen increases the risk for endometrial cancer. Evidence is insufficient to determine the effects of unopposed estrogen on the risk for breast and ovarian cancer, CHD, dementia and cognitive function, or mortality. As a result, the USPSTF could not determine whether the benefits of unopposed estrogen outweigh the harms for women who have had a hysterectomy. Better data on benefits and harms are expected from ongoing randomized trials, including the Women's Health Initiative (WHI) study of unopposed estrogen in women who have had a hysterectomy (1).

CLINICAL CONSIDERATIONS

Although the USPSTF concludes that the harms of estrogen–progestin therapy are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest. Some women, depending on their risk characteristics and personal preferences, might decide that the benefits of taking HRT outweigh the potential harms. Based on results reported from the WHI study (1) for women ages 50 to 79 years (average age, 63 years), 10 000 women taking estrogen and progestin for 1 year, might experience 7 additional CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, but would also have 6 fewer cases of colorectal cancer and 5 fewer hip fractures.

Clinicians should develop a shared decision-making approach to preventing chronic diseases in perimenopausal and postmenopausal women. This approach should consider individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Clinicians should discuss with patients other effective strategies for preventing osteoporosis and fractures (see other USPSTF recommendations available on the USPSTF Web site: Screening for Postmenopausal Osteoporosis, Screening for Hypertension, Screening Adults for Lipid Disorders, Counseling To Prevent Tobacco Use, Counseling To Promote a Healthy Diet, Counseling To Promote Physical Activity, Screening for Breast Cancer, and Screening for Colorectal Cancer).

The USPSTF did not consider the use of HRT for the management of menopausal symptoms. Decisions to initiate or continue HRT for menopausal symptoms should be made on the basis of discussions between a woman and her clinician. Women should be informed that there are some risks (such as the risk for venous thromboembolism, CHD, and stroke) within the first 1 to 2 years of therapy, whereas other risks (such as the risk for breast cancer) appear to increase with longer-term HRT. Other expert groups have recommended that women who decide to take HRT for the relief of menopausal symptoms use the lowest effective dose for the shortest possible time.

The quality of evidence on the benefits and harms of HRT varies for different hormone regimens. Other than the two large randomized, controlled trials of daily conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), most of the evidence on HRT comes from observational studies that did not differentiate among the effects of specific hormone preparations (1, 2). Until data indicate that other HRT regimens have a favorable balance of benefits to harms, a cautious approach would be to avoid using HRT routinely for the specific purpose of preventing chronic disease in women.

Evidence is inconclusive to determine whether phytoestrogens (isoflavones such as iproflavone, which are found in soy milk, soy flour, tofu, and other soy products) are effective for reducing the risk for osteoporosis or cardiovascular disease (USPSTF Unpublished data, 2002).

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Consequences

Hormone replacement therapy is one of the most commonly prescribed drug regimens for postmenopausal women in the United States. Many women use HRT to treat symptoms of menopause, but publicity about the possible ability of HRT to prevent chronic conditions, such as osteoporosis, CHD, Alzheimer disease, and colorectal cancer, has also contributed to the increase in HRT use over the past decade.

The median age of menopause in women in the United States is 51 years (range, 41 to 59 years), but ovarian production of estrogen and progestin begins to decrease years before the complete cessation of menses. Lower levels of circulating estrogen contribute to the accelerated bone loss and increased low-density lipoprotein levels that occur around menopause. The average woman in the United States who reaches menopause has a life expectancy of nearly 30 years. The probability that a menopausal woman will develop various chronic diseases over her lifetime has been estimated to be 46% for CHD, 20% for stroke, 15% for hip fracture, 10% for breast cancer, and 2.6% for endometrial cancer (2). In North America, an estimated 7% to 8% of persons 75 to 84 years of age have dementia, and postmenopausal women have a 1.4- to 3.0-fold higher risk for Alzheimer disease than do men. The lifetime risk for developing colorectal cancer for a woman in the United States is 6%, with more than 90% of cases occurring after 50 years of age (3). Many of these causes of morbidity in older women appear to be influenced by estrogen or progestin.

Osteoporosis affects a large proportion of postmenopausal women in the United States, and the prevalence of osteoporosis increases steadily with age. In the postmenopausal period, decline of estrogen production is associated with reduction of bone mineral density. Bone density is estimated to decrease by 2% each year during the first 5 years after menopause, followed by an annual loss of approximately 1% for the rest of a woman's life. On the basis of commonly used criteria, up to 70% of women older than 80 years of age have osteoporosis.

Benefits of Hormone Replacement Therapy

Osteoporosis and Fractures

Low bone density is associated with an increased risk for osteoporotic fractures. Good evidence from observational studies and randomized clinical trials demonstrates that estrogen therapy increases bone density and reduces risk for fractures. Good evidence from many randomized clinical trials has demonstrated that HRT increases bone density at the hip, the lumbar spine, and peripheral sites. A meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (relative risk [RR], 0.73 [95% CI, 0.56 to 0.94]), although the quality of individual studies varied (4). Observational studies have also demonstrated reductions in fractures of the vertebrae (RR for ever use, 0.6 [95% CI, 0.36 to 0.99]), wrist (RR for current use, 0.39 [95% CI, 0.24 to 0.64]), and possibly hip (RR for current use, 0.64 [95% CI, 0.32 to 1.04]) among women taking HRT. The Heart and Estrogen/progestin Replacement Study (HERS and its unblinded follow-up study, HERS II) (5), a trial of combined estrogen and progestin (CEE/MPA) for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04 [95% CI, 0.87 to 1.25]). The WHI (1) found significant reductions in total fracture risk (RH, 0.76 [95% CI, 0.63 to 0.92]) among healthy women taking estrogen and progestin. The WHI also reported reductions for hip (RH, 0.66 [95% CI, 0.33 to 1.33]) and vertebral fracture (RH, 0.66 [95% CI, 0.32 to 1.34]), although these did not achieve statistical significance in adjusted analyses (1). The WHI reported both nominal and adjusted confidence intervals. The USPSTF relied on nominal confidence intervals for the primary outcomes of breast cancer and CHD and adjusted confidence intervals for other secondary outcomes. The USPSTF concluded that there was good evidence that HRT increases bone mineral density and fair to good evidence that it reduces fractures.

Colorectal Cancer

A meta-analysis of 18 observational studies of postmenopausal women reported a 20% reduction in cancer of the colon (RR, 0.80 [95% CI, 0.74 to 0.86]) and a 19% reduction in cancer of the rectum (RR, 0.81 [95% CI, 0.72 to 0.92]) among women who had ever used HRT (6). This decrease in risk was more apparent when current users were compared with those who had never used HRT (RR, 0.66 [95% CI, 0.59 to 0.74]). Comparable results from the WHI study were reported for women taking CEE/MPA (RH, 0.63 [95% CI, 0.32 to 1.24]) (1), and HERS also found reduced incidence of colon cancer (RH, 0.8 [95% CI, 0.46 to 1.45]) (5). The USPSTF concluded that there was fair evidence that HRT reduces colorectal cancer incidence.

Uncertain Benefits or Harms of Hormone Replacement Therapy

Cognition and Dementia

Nine randomized, controlled trials examining the effect of HRT on cognition showed improvement in verbal memory, vigilance, reasoning, and motor speed among women who had menopausal symptoms but not among women who were asymptomatic at baseline. Because of heterogeneity and variation in assessment of outcomes among studies, meta-analysis of these studies was not performed for the USPSTF (7). A meta-analysis of 12 observational studies (1 of good quality, 3 of fair quality, and 8 of poor quality) showed a reduction in the risk for dementia among postmenopausal women taking HRT (RR, 0.66 [95% CI, 0.53 to 0.82]) (8). Neither the WHI nor HERS has yet reported effects of HRT on cognition and dementia, but other ongoing trials are examining the effects of HRT on these end points. Given the methodologic limitations of the available studies and the potential for confounding or selection bias, the USPSTF concluded that there is insufficient evidence to determine whether HRT reduces the risk for dementia or cognitive dysfunction in otherwise healthy women.

Harms of Hormone Replacement Therapy

Breast Cancer

Because breast tissue is sensitive to reproductive hormones, there has been long-standing concern about breast cancer risk among women who take HRT. The estrogen and progestin arm of the WHI study was recently terminated because of an increased breast cancer incidence (RH, 1.26 [95% CI, 1.00 to 1.59]) (1). However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of follow-up in HERS (RH, 1.27 [95% CI, 0.84 to 1.94]) (5). Although many good observational studies on breast cancer and meta-analyses of these studies have been conducted, the conclusions are limited by healthy-user bias; variations in specific preparations, dose, and duration of estrogen and progestin therapy; and differences in the ways in which breast cancer end points were ascertained. In the aggregate, breast cancer incidence is slightly increased for current (RR, 1.21 to 1.40) or long-term (>5 years) users (RR, 1.23 to 1.35) compared with nonusers (7, 9, 10). However, there seems to be no effect on or decreased breast cancer mortality in ever- or short-term users (RR, 0.5 to 1.0) (10). The effects of long-term HRT use on breast cancer mortality in two good-quality cohort studies are conflicting (11, 12). Whether the combination of estrogen and progestin confers a greater risk than estrogen alone is unknown; WHI investigators have reported that no increase in breast cancer has been observed after 5 years of follow-up in the ongoing study of unopposed estrogen in women who have had a hysterectomy. The USPSTF concluded that there was fair to good evidence that HRT increases the incidence of breast cancer (with best evidence for estrogen plus progestin), but its effects on breast cancer mortality are uncertain.

Coronary Heart Disease

Coronary heart disease remains the leading cause of death among women. Hormone replacement therapy has diverse effects on lipid levels, endothelial-wall function, blood pressure, coagulation factors, weight, and inflammation (for example, C-reactive protein). In the WHI study (1), women who took CEE/MPA daily had an increased risk for CHD (fatal and nonfatal myocardial infarctions), which was evident shortly after initiation of the study (RH, 1.29 [95% CI, 1.02 to 1.63]). Coronary heart disease mortality was not significantly increased (RH, 1.18 [95% CI, 0.70 to 1.97]). Meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80 [95% CI, 0.68 to 0.95]) among current HRT users, but not among ever or past users, compared with women who had never taken HRT (nonusers) (7, 13). However, among studies that controlled for socioeconomic status (social class, education, or income), no benefit was seen among current HRT users (RH, 0.97 [95% CI, 0.82 to 1.16]), suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (for example, exercise, alcohol use) rather than use of HRT. Coronary heart disease mortality in observational studies is reduced among current HRT users (RR, 0.62 [95% CI, 0.40 to 0.90]) but is not reduced among ever, past, or all users. Thus, selection bias (the tendency of healthier women to use HRT) appears to explain the apparent protective effect of estrogen on CHD seen in observational studies. The USPSTF concluded that HRT does not decrease, and may in fact increase, the incidence of CHD. The effects of HRT on CHD mortality, however, are less certain.

Stroke

A meta-analysis of nine observational primary prevention studies suggests that HRT use is associated with a small increase in stroke incidence (RR, 1.12 [95% CI, 1.01 to 1.23]), due primarily to an increase in thromboembolic stroke (RR, 1.20 [95% CI, 1.01 to 1.40]) (13, 14). The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81 [95% CI, 0.71 to 0.92]). These results are consistent with findings from the estrogen and progestin arm of the WHI (1), which reported increased incidence of stroke in women taking CEE/MPA daily (RH, 1.41 [95% CI, 0.86 to 2.31]). Two secondary prevention trials (15, 16), which were not included in the USPSTF review of HRT for primary prevention, reported no clear effect of HRT on stroke incidence, but stroke mortality was increased in women with a previous stroke (16). The USPSTF concluded that there is fair evidence that HRT increases the risk for stroke.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized, controlled trials; 8 case–control studies; and 1 cohort study), HRT was associated with an increased risk for venous thromboembolism (RR, 2.14 [95% CI, 1.64 to 2.81]) (17, 18). Five of six studies that examined the effects of HRT over time reported that the risk was highest within the first year of use (RR, 3.49 [95% CI, 2.33 to 5.59]). These results are consistent with the findings in the estrogen and progestin arm of the WHI, which reported a twofold increased rate of venous thromboembolic disease (RH, 2.11 [95% CI, 1.26 to 3.55]), including deep venous thrombosis and pulmonary embolism, in women taking CEE/MPA daily (1). The USPSTF concluded that there is good evidence that HRT increases the risk for venous thromboembolism.

Endometrial and Ovarian Cancer

Results of a previously published meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk of 2.3 (95% CI, 2.1 to 2.5) for users of unopposed estrogen compared with nonusers (19). Risks increased with increasing duration of use (RR, 9.5 for 10 years of use). The risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy in these studies. With combined estrogen–progestin regimens, cohort studies showed a decreased risk for endometrial cancer (RR, 0.4 [95% CI, 0.2 to 0.6]) compared with nonusers, but case–control studies showed an increase in risk (odds ratio [OR], 1.8 [95% CI, 1.1 to 3.1]). Estrogen and progestin did not increase the risk for endometrial cancer in HERS (RH, 0.25 [95% CI, 0.05 to 1.18]) (4) or in the WHI (RH, 0.83 [95% CI, 0.29 to 2.32]) (1). The USPSTF concluded that unopposed estrogen, but not combined estrogen–progestin therapy, increases risk for endometrial cancer.

Data on the association between the use of HRT and the risk for ovarian cancer are inconsistent. Results of case–control studies have been mixed, but two good-quality cohort studies reported increased risks (RR, 1.8 to 2.2) for ovarian cancer or ovarian cancer mortality among women who had taken HRT for 10 years or more (20, 21); a third study found no effect of HRT on ovarian cancer mortality (22). One study suggested higher risk with unopposed estrogen than with estrogen–progestin therapy (20), but data are insufficient to resolve the effects of different formulations or doses of HRT on ovarian cancer risk. Neither the WHI nor HERS has reported risk for ovarian cancer. The USPSTF concluded that evidence was insufficient to determine the effect of HRT on ovarian cancer.

Cholecystitis

Many but not all studies have reported an association between HRT and gallbladder disease. Results from a good-quality cohort study, the Nurses' Health Study, reported an increase in risk for cholecystitis among current HRT users (RR, 1.8 [95% CI, 1.6 to 2.0]) and long-term users (>5 years) (RR, 2.5 [95% CI, 2.0 to 2.9]) compared with nonusers (23). Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of follow-up was reported among women taking estrogen plus progestin compared with those taking placebo (RR, 1.48 [95% CI, 1.12 to 1.95]) in HERS (5, 24); the WHI has not reported biliary tract outcomes. The USPSTF concluded that there is fair evidence that HRT increases the risk for cholecystitis.

DISCUSSION

Most women begin HRT to relieve symptoms of menopause. Many women, however, have continued to take HRT because earlier studies indicated that HRT could prevent osteoporosis, heart disease, and possibly other chronic diseases. More recent, higher-quality studies have confirmed the benefits of HRT in preventing osteoporosis and fractures. These studies, however, demonstrated that HRT does not reduce, and may actually increase, the risk for CHD, and they confirmed previously suspected harms of HRT. Therefore, the calculus of benefits and harms has changed. Important questions about the effects of dose, duration, and specific preparations of hormone therapy remain. For an individual woman, the balance of benefits and harms may vary. Women considering taking HRT for prevention should make that decision with their clinician in the context of a discussion of benefits and harms of HRT and alternatives to HRT for the prevention of chronic diseases.

RECOMMENDATIONS OF OTHERS

Most organizations with guidelines on postmenopausal HRT have revised or are revising their recommendations in light of the findings of recently reported clinical trials. The American College of Obstetricians and Gynecologists (25) and the North American Menopause Society (26) recommend against the use of HRT for the primary or secondary prevention of cardiovascular disease. Both organizations recommend caution in using HRT solely to prevent osteoporosis and suggest that alternative therapies should also be considered. Both organizations consider HRT an acceptable treatment option for menopausal symptoms but advise caution about the prolonged use of HRT for the relief of symptoms. The American Heart Association now recommends against the use of HRT for primary or secondary prevention of cardiovascular disease (27). The American College of Preventive Medicine (28), the American Association of Clinical Endocrinologists (29), and the American Academy of Family Physicians (30) have previously recommended counseling perimenopausal and menopausal patients about the benefits and harms of HRT based on the individual risks for a particular patient, but these organizations have not yet revised their recommendations in light of the findings of recently reported trials. The Canadian Task Force on Preventive Health Care is updating its assessment of the effect of HRT on cardiovascular disease and cancer (31).

APPENDIX

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Appendix Table 1. **U.S. Preventive Services Task Force Grades and Recommendations***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

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Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache

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Migraine headache is a common disorder seen in primary care. It affects 18% of women and 6.5% of men in the United States, almost half of whom are undiagnosed or undertreated (1, 2). These guidelines, developed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine, with assistance from the American Headache Society, are based on two previously published papers (3, 4). The papers, titled "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management of Acute Attacks," by Matchar and colleagues (3), and "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine," by Ramadan and coworkers (4), can be found at www.aan.com/professionals/practice/guidelines.cfm.[1]

The target audience for this guideline is primary care physicians. The guideline applies to patients with acute migraine attacks, with or without aura, and patients with migraine who are candidates for preventive drug therapy. Although these guidelines are all based on the articles by Matchar and Ramadan and colleagues, the recommendations may differ because different thresholds of evidence were needed for making a positive recommendation. **Table 1** compares the AAFP/ACP–ASIM guideline and the U.S. Headache Consortium Guideline.

Throughout the text, asterisks indicate drugs that are currently not available in the United States.

DIAGNOSIS

Headache has many potential causes. Most headaches are caused by the primary headache disorders, which include migraine, cluster, and tension-type headaches. Secondary headaches, which are those with underlying pathologic causes, are far less common. Migraine is a chronic condition with recurrent acute attacks whose characteristics vary among patients and often among attacks within a single patient. Migraine is a syndrome with a wide variety of neurologic and non-neurologic manifestations. The International Headache Society (6) has developed diagnostic criteria for migraine with and without aura (**Appendix Table 1**). This classification system serves to diagnose headache syndromes, not patients. Thus, one patient could have more than one type of headache disorder. For example, it is not uncommon for migraine patients to also have episodic tension-type headaches.

MANAGEMENT OF ACUTE ATTACKS

Effective long-term management of patients with migraine is challenging because of the complexity of the condition. Experts suggest several goals for successful treatment of acute attacks of migraine. These include treating attacks rapidly and consistently to avoid headache recurrence, to restore the patient's ability to function, and to minimize the use of backup and rescue medications.

Clinicians need to educate people with migraine about their condition and its treatment and encourage them to participate in their own management. The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms. Patient input can provide the best guide to treatment selection and helps the physician to better understand and accommodate patient treatment goals. Developing an effective acute migraine management strategy can be complex, and an engaged patient is more likely to negotiate this process successfully. Encouraging patients to identify and avoid triggers (**Table 2**) and to be actively involved in their own management by tracking their own progress may be especially useful.

Once a diagnosis of migraine is established, patients

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[1] In an effort to educate clinicians and patients about headache's impact, diagnosis, management, and prognosis, the U.S. Headache Consortium was founded in 1996. The Consortium was made up of seven member organizations representing primary care, emergency medicine, neurology, and headache specialists. The objective of the U.S. Headache Consortium was to develop scientifically sound, clinically relevant practice guidelines on chronic headache, particularly migraine, in the primary care setting. Five documents on headache and migraine were produced. These documents can be found on the American Academy of Neurology Web site (www.aan.com).

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and their health care providers should decide together how to treat acute attacks and whether the patient is a candidate for preventive medications. A wide range of acute treatments with varying efficacies is currently in use (**Appendix Table 2**, available at www.annals.org). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy in the management of acute migraine headache. It also provides a clear understanding of the adverse events associated with various agents.

The Headache Consortium's review of the evidence on antiemetics, barbiturate hypnotics, ergot alkaloids and derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), combination analgesics and nonopiate analgesics, opiate analgesics, triptans, and other agents found good evidence of the efficacy of only a few agents in the treatment of acute migraine (3).

Available Agents

NSAIDs

Their demonstrated efficacy and favorable tolerability make NSAIDs a first-line treatment choice for all migraine attacks, including severe attacks that have responded to NSAIDs in the past. Among the NSAIDs, the most consistent evidence exists for aspirin (8–10), ibuprofen (11, 12), naproxen sodium (13, 14), tolfenamic acid* (8, 15), and the combination agent acetaminophen plus aspirin plus caffeine for the acute treatment of migraine (16). The evidence shows that acetaminophen alone is ineffective (17).

Serotonin$_{1B/1D}$ Agonists (Triptans)

There is good evidence for the effectiveness of the oral triptans naratriptan (18, 19), rizatriptan (20–23), sumatriptan (24–31), and zolmitriptan (32–34). In addition, there is good evidence for the effectiveness of subcutaneous (35–38) and intranasal (39–41) sumatriptan, making it an option for patients with nausea and vomiting. Adverse effects of the triptans include chest symptoms, but postmarketing data indicate that true ischemic events are rare. Triptans are contraindicated in patients with risk for heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension. Subcutaneous sumatriptan is associated with a very rapid onset of action, and oral naratriptan is associated with a slower onset of action.

Ergotamines

There is good evidence for the efficacy and safety of intranasal dihydroergotamine (DHE) as monotherapy for acute migraine attacks (42–46). Placebo-controlled studies of intravenous DHE did not clearly establish its efficacy in the acute treatment of migraine (47, 48). The evidence was inconsistent to support efficacy of ergotamine or ergotamine–caffeine, and the studies documented frequent adverse events.

Opioids

It is well recognized that opiates are good analgesics, but there is good evidence only for the efficacy of butorphanol nasal spray (49, 50). Although opioids are commonly used, surprisingly few studies of opioid use in headache pain document whether overuse and the development of dependence are as frequent as clinically perceived. Until further data are available, these drugs may be better reserved for use when other medications cannot be used, when sedation effects are not a concern, or the risk for abuse has been addressed.

Other Agents

Fair evidence suggests that the antiemetic metoclopramide, given intravenously, may be an appropriate choice as monotherapy for acute attacks (51–53), particularly in patients with nausea and vomiting when the sedating side effect may also be useful. Isometheptene and isometheptene combinations obtained only borderline significance in relieving headache pain (17, 54, 55). Other agents used in practice, such as intravenous corticosteroids and intranasal lidocaine, are not effective.

Choice of Treatment

Since patient responses to these therapies are not always predictable, individualized management is important. The choice of treatment should be based on, among other characteristics, the frequency and severity of attacks; the presence and degree of temporary disability; and the profile of associated symptoms, such as nausea and vomiting. The patient's history of, response to, and tolerance for specific medications must also be considered. Coexisting conditions (such as heart disease, pregnancy, and uncontrolled hypertension) may limit treatment choices.

No studies document the effectiveness of specific treatment schedules, but experts suggest that acute therapy should be limited to no more than two times per week to guard against medication-overuse headache (or drug-induced headache). Medication-overuse headache is thought to result from frequent use of acute medication and has a pattern of increasing headache frequency, often resulting in daily headaches. In patients with suspected medication overuse or patients at risk for medication overuse, preventive migraine therapy should be considered.

Although some use the term ***rebound headache*** interchangeably with the term ***medication-overuse headache***, rebound headache is a distinct entity. Rebound headache is associated with withdrawal of analgesics or abortive migraine medication. There is no uniform agreement about which agents can cause rebound headache, although ergotamine (not DHE); opiates; triptans; and simple and mixed analgesics containing butalbital, caffeine, or isometheptene

Table 1. **Summary of U.S. Headache Consortium Recommendations Compared with AAFP/ACP–ASIM Recommendations***

Treatment Type	U.S. Headache Consortium Recommendations	AAFP/ACP–ASIM Recommendations
Acute	Use migraine-specific agents (triptans, DHE, ergotamine) in patients with severe migraine and in patients whose migraines respond poorly to NSAIDs or combination analgesics such as aspirin + acetaminophen + caffeine. Recommended medications based on at least two double-blind, placebo-controlled trials and clinical impression of effect: Oral acetaminophen + aspirin + caffeine Oral aspirin IN Butorphanol SC, IM, IV, IN DHE IV DHE + antiemetic Oral ibuprofen Oral naproxen sodium Oral naratriptan IV prochlorperazine Oral rizatriptan SC, IN, oral sumatriptan Oral zolmitriptan	Use NSAIDs as first-line therapy. Recommended agents: Aspirin Ibuprofen Naproxen sodium Tolfenamic acid† Acetaminophen + aspirin + caffeine In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents: DHE nasal spray Oral naratriptan SC, oral sumatriptan Oral rizatriptan Oral zolmitriptan
	Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.	Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea and vomiting with an antiemetic.
	Consider a self-administered rescue medication for patients with severe migraine that does not respond well to or fails other treatments‡.	
	Guard against medication-overuse headache.	
	Educate patients with migraine about their condition and its treatment, and encourage them to participate in their own management	Educate patients with migraine about their condition and its treatment, and encourage them to participate in their own management
Preventive	Medication use Initiate treatment with lowest effective dose Give each treatment an adequate trial Avoid interfering medications Use a long-acting formulation to improve adherence	Patients with migraine should be evaluated for use of preventive therapy. Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability that lasts 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) use of abortive medication more than twice per week; or 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.
	Recommended agents found to have medium to high efficacy and mild or infrequent side effects: Amitriptyline Divalproex sodium Lisuride† Propranolol Timolol	Recommended first-line agents, currently available in the United States, for the prevention of migraine headache: Propranolol (80–240 mg/d) Timolol (20–30 mg/d) Amitriptyline (30–150 mg/d) Divalproex sodium (500–1500 mg/d) Sodium valproate (800–1500 mg/d)
	Recommended agents found to have medium to high efficacy but with side effect concerns: Methysergide Flunarizine† Pizotifen† Time-released DHE*	Other medications with proven efficacy but limited published data on adverse events, or frequent or severe adverse events: Flunarizine† Lisuride† Pizotifen† Time-released DHE† Methysergide
	Recommended agents based on consensus and clinical experience: Cyprohetadine Buproprion Diltiazem Doxepin Fluvoxamine Ibuprofen Imipramine Mirtazepine Nortriptyline Paroxetine Protriptyline	

Continued on following page

Table 1—**Continued**

Treatment Type	U.S. Headache Consortium Recommendations	AAFP/ACP–ASIM Recommendations
Preventive *(continued)*	Sertraline Tiagabine Topiramate Trazadone Venlafaxine	
	Patient education Maximize adherence Address patient expectations Create a formal management plan	Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan. Therapy should be reevaluated on a regular basis.
	Evaluation Monitor patients' headaches by having them keep headache diaries Reevaluate therapy	Encourage patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example. Diaries should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.
	Comorbid conditions Once a coexisting condition is identified, select a pharmacologic agent that will treat both disorders Establish that the coexisting condition is not a contraindication to the selected migraine therapies and that the therapy will not exacerbate the migraine	

* Consortium recommendations are based on references 3 and 4. The ACP–ASIM historically has not used a grading system for guideline recommendations because its development process mandates the use of only high-quality evidence (that is, randomized, controlled trials or "A"-level evidence) as a basis for recommendations. AAFP = American Academy of Family Physicians; ACP–ASIM = American College of Physicians–American Society of Internal Medicine; DHE = dihydroergotamine; IM = intramuscular; IN = intranasal; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; SC = subcutaneous.

† Currently not available in the United States.

‡ Rescue medication is an agent (e.g., an opioid) that the patient can use at home when other treatments have failed.

are generally thought to do so. There is less uniform opinion about other antimigraine agents.

Another clinical consideration is the use of a self-administered rescue medication for patients with severe migraine attack that is not responding to (or failing) other treatments. A rescue medication is an agent such as an opioid or a butalbital-containing compound that the patient can use at home when other treatments have failed. Although rescue medications often do not completely eliminate pain and allow patients to return to normal activities, they permit the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department. A cooperative arrangement between provider and patient may extend to the use of rescue medication in appropriate situations.

Summary of Treatment of Acute Migraine

A body of evidence now points to effective first- and second-line agents for acute treatment of migraine. Beyond the choice of agent lies the choice of management strategy. Recently, interest and research in step care versus stratified care have increased. Step care refers to the initial use of safe, effective, and inexpensive medications as first-line agents in acute attacks of any severity. If the initial agent fails, a second-line, more expensive, migraine-specific medication is then used. The stratified care model initially stratifies migraine attacks by severity, advocating migraine-specific agents for moderate to severe attacks, regardless of previous response to or an unknown response to other agents. Which approach is more effective is still an open question (56).

MANAGEMENT OF MIGRAINE WITH PREVENTIVE THERAPY

Once patients and their health care providers decide how to treat acute attacks, use of preventive medications should be considered. Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) the use of abortive medication more than twice per week; and 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. Other factors to consider are adverse events with acute therapies, patient preference, and the cost of both acute and preventive therapies. (The U.S. Headache Consortium also produced a document on behavioral and other nonpharmacologic therapies for headache prevention, which can be found at www.aan.com/professionals/practice/guidelines.cfm.)

A wide range of preventive treatments with varying efficacies is currently in use (**Appendix** Table 3, available at www.annals.org). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy in the prevention of migraine headache. It also provides a clear understanding of the adverse events associated with various agents. The Headache Consortium's review of the evidence on α_2-agonists, anticonvulsants, antidepressants, β-blockers, calcium-channel blockers, NSAIDs, serotonergic agents (ergot derivatives, methysergide, and others), hormone therapy, feverfew, magnesium,

Table 2. **Some Commonly Reported Triggers of Migraine Headache***

- Food triggers
  - Alcohol
  - Caffeine
  - Chocolate
  - Monosodium glutamate
  - Tyramine-containing foods
  - Nitrate-containing foods
- Behavioral–physiologic triggers
  - Too much or too little sleep
  - Skipped meals
  - Stress or post-stress
  - Menstruation
  - Fatigue
  - Physical activity
- Environmental triggers
  - Loud noises
  - Weather changes
  - Perfumes or fumes
  - High altitude
  - Exposure to glare or flickering lights

* Adapted from reference 7.

and riboflavin found that there was good evidence of the efficacy of only a few agents in migraine prevention. A summary of these results follows.

Available Agents

β-Blockers

Evidence consistently showed the efficacy of propranolol, 80 to 240 mg/d (57–63), and timolol, 20 to 30 mg/d (63–65), for the prevention of migraine. One trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was superior for patients with mixed migraine and tension-type headache (66). There is limited evidence of a moderate effect for atenolol (67, 68), metoprolol (69–71), and nadolol (72–74). β-Blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) seem to be ineffective for the prevention of migraine. Adverse effects reported most commonly with β-blockers were fatigue, depression, nausea, dizziness, and insomnia. These symptoms appear to be fairly well tolerated and seldom caused premature withdrawal from trials.

Antidepressants

Amitriptyline has been more frequently studied than the other antidepressants and is the only one with consistent support for efficacy in migraine prevention (75–77). The dosages that were most efficacious in the clinical trials ranged from 30 to 150 mg/d. Drowsiness, weight gain, and anticholinergic symptoms were frequently reported with the tricyclic antidepressants studied, including amitriptyline. There is no evidence for the use of nortriptyline, protriptyline, doxepin, clomipramine, or imipramine. There is limited evidence of a modest effect for fluoxetine at dosages ranging from 20 mg every other day to 40 mg per day (78, 79). There is no evidence from controlled trials for the use of fluvoxamine, paroxetine, sertraline, phenelzine, bupropion, mirtazapine, trazodone, or venlafaxine.

Anticonvulsants

For the anticonvulsants, there is good evidence for the efficacy of divalproex sodium (80–82) and sodium valproate (83, 84). Adverse events with these therapies are not uncommon and include weight gain, hair loss, tremor, and teratogenic potential, such as neural tube defects. These agents may be especially useful in patients with prolonged or atypical migraine aura. Carbamazepine and vigabatrin* have been shown to be ineffective, and there is limited evidence for moderate efficacy of gabapentin (85).

NSAIDs

A meta-analysis (4) of five of seven placebo-controlled trials of naproxen or naproxen sodium showed a modest effect on headache prevention (62, 86–92). Similar trends were observed in single placebo-controlled trials of flurbiprofen, indobufen*, ketoprofen, lornoxicam*, and mefenamic acid and in two trials of tolfenamic acid*. Placebo-controlled trials of aspirin, aspirin plus dipyridamole, fenoprofen, and indomethacin were inconclusive. There is no evidence for the use of ibuprofen or nabumetone in the prevention of migraine.

Side effect rates for naproxen were not significantly higher than those seen with placebo. The most commonly reported adverse events with all NSAIDs were gastrointestinal symptoms, including nausea, vomiting, gastritis, and blood in the stool. In the trials reviewed, such symptoms were reported by 3% to 45% of participants (86).

Serotonergic Agents

Of these agents, time-released DHE* had the strongest support, with consistently positive findings in four placebo-controlled trials (93–96). Evidence is insufficient for the efficacy of ergotamine or ergotamine plus caffeine plus butalbital plus belladonna alkaloids or methylergonovine for migraine prevention. Limited information was reported on adverse events associated with these agents. The most commonly reported events for all the ergot alkaloids were gastrointestinal symptoms.

There is strong evidence for the efficacy of methysergide (97–100), a semisynthetic ergot alkaloid. However, there are reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted administration. The manufacturer suggests that methysergide therapy be discontinued for 3 to 4 weeks after each 6-month course of treatment. Other adverse events most commonly reported included gastrointestinal symptoms and leg symptoms (restlessness or pain).

Other serotonergic agents that have been evaluated for the prevention of migraine include pizotifen*, lisuride*, oxitriptan*, iprazochrome*, and tropisetron*. Only lisuride (101–104) and pizotifen (87, 99, 105–110) have consistent evidence that supports their efficacy in the prevention of migraine. Published data on adverse events associated with lisuride are limited, and pizotifen is often associated with weight gain and drowsiness.

Calcium-Channel Blockers

The evidence for nifedipine, nimodipine, cyclandelate*, and verapamil is poor quality and difficult to interpret, suggesting only a modest effect (see reference 4 for study references). There is no evidence for the use of diltiazem in the prevention of migraine. Symptoms reported with these agents included dizziness, edema, flushing, and constipation.

Flunarizine*, 10 mg/d, has proven efficacy in the prevention of migraine and is commonly used in countries where it is available (111–115). Adverse events reported with flunarizine include sedation, weight gain, and abdominal pain. Depression and extrapyramidal symptoms can be observed, particularly in elderly persons.

α_2-Agonists

There is good evidence for the lack of efficacy of the α_2-agonist clonidine in the prevention of migraine (116–120). Limited evidence shows moderate efficacy of guanfacine (121).

Hormone Therapy, Feverfew, Magnesium, and Riboflavin

There is fair evidence for modest efficacy of these agents in certain circumstances, but more trials need to be done. Most of the existing trials had small sample sizes, had self-referred or special patient samples, or had other methodologic flaws (see reference 4 for more details and references).

Summary of Preventive Therapy

To alleviate the suffering of many patients with migraine, clinicians need to be aware of the commonly accepted indications for preventive therapy and initiate effective therapy in those patients. Although many agents are available for the preventive treatment of migraine, only a few have proven efficacy. Once an agent has been chosen, clinicians should initiate therapy with a low dose and titrate the dose slowly up until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. Because a clinical benefit may take as long as 2 to 3 months to manifest, each treatment should be given an adequate trial. Once preventive treatment is under way, interfering medications, such as overused acute medications such as ergotamine, should be avoided. After a period of stability, clinicians should consider tapering or discontinuing treatment. Patient and clinician need to engage in an ongoing dialogue in which patient expectations and goals for therapy are taken into account when agents are chosen, titrated, or discontinued.

RECOMMENDATIONS

Recommendation 1: For most migraine sufferers, nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy.

To date, the most consistent evidence exists for aspirin, ibuprofen, naproxen sodium, tolfenamic acid*, and the combination agent acetaminophen plus aspirin plus caffeine. There is no evidence for the use of acetaminophen alone.

Recommendation 2: In patients whose migraine attack has not responded to NSAIDs, use migraine-specific agents (triptans, DHE).

There is good evidence for the following triptans: oral naratriptan, rizatriptan, and zolmitriptan; oral and subcu-

Appendix Table 1. **International Headache Society Classification***

Migraine without aura
  A. At least five attacks fulfilling criteria B, C, and D
  B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
  C. Headache with at least two of the following characteristics
    Unilateral location
    Pulsating quality
    Moderate or severe intensity (inhibits or prohibits daily activities)
    Aggravation by walking stairs or performing similar routine physical activity
  D. During headache, at least one of the following events
    Nausea and/or vomiting
    Photophobia and phonophobia
  E. At least one of the following scenarios
    History and physical and neurologic examination do not suggest one of the disorders causing secondary headaches.
    History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations.
    One of such disorders is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.
Migraine with aura
  A. At least two attacks fulfilling criterion B
  B. At least three of the following four characteristics
    One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
    At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
    No aura symptom lasting more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased.
    Headache following aura with a free interval of less than 60 minutes (It may also begin before or simultaneously with the aura.)
  C. At least one of the following:
    History and physical and neurologic examinations do not suggest one of the following disorders:
      Headache associated with head trauma
      Headache associated with vascular disorders
      Headache associated with nonvascular intracranial disorder
      Headache associated with substances or their withdrawal
      Headache associated with noncephalic disorder
      Headache associated with metabolic disorder
      Headache or facial pain associated with disorders of the cranium; neck; or ear, nose, and throat
      Cranial neuralgias
    History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations.
    Such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

* For migraine without aura, headaches must meet criterion A; those five attacks must fulfill criteria B through D *and* must fulfill at least one of the criteria under E. For migraine with aura, headaches must meet criterion A; those two attacks must fulfill criteria B *and* at least one of those listed under C. Adapted from reference 6.

taneous sumatriptan; and DHE nasal spray. Few data in the literature demonstrate which triptans are more effective. Oral opiate combinations and butorphanol may be considered in acute migraine when sedation side effects are not a concern and the risk for abuse has been addressed.

Recommendation 3: Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea and vomiting with an antiemetic.

Evidence is limited, but in some patients, concomitant treatment with an antiemetic and an oral migraine medication may be appropriate. Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.

Recommendation 4: Migraine sufferers should be evaluated for use of preventive therapy.

Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) use of abortive medication more than twice per week; or 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Recommendation 5: Recommended first-line agents for the prevention of migraine headache are propranolol (80 to 240 mg/d), timolol (20 to 30 mg/d), amitriptyline (30 to 150 mg/d), divalproex sodium (500 to 1500 mg/d), and sodium valproate (800 to 1500 mg/d).

Medications with proven efficacy but limited published data on adverse events or frequent or severe adverse events include flunarizine*, lisuride*, pizotifen*, time-released DHE*, and methysergide.

Recommendation 6: Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan. Therapy should be reevaluated on a regular basis.

There is strong consensus about the need for educating people with migraine. The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms, such as medication-overuse headache. Encouraging patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example, may be especially useful. Diaries should measure attack frequency, severity, and duration; resulting disability; response to type of treatment; and adverse effects of medication. Patient input can provide the best guide to treatment selection.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP–ASIM clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Health Care–Associated Bloodstream Infections: A Change in Thinking

It is not necessary to change. Survival is not mandatory.

—W. Edwards Deming

Nosocomial, or hospital-acquired, bloodstream infections (BSIs) are an important cause of morbidity and mortality, affecting more than 200 000 patients per year in the United States (1). These infections are often associated with the use of catheters. Catheter-related infections make up about 14% of all hospital-acquired infections (2) and are responsible for more hospital days and death than any other hospital-acquired infection (3). Bloodstream infections can be primary or secondary. A primary infection is an infection directly into the vascular system; a secondary infection originates at a site other than the vascular system, such as the urinary tract, respiratory tract, or wounds, and spreads to the vascular system. According to the definitions from the Centers for Disease Control and Prevention (CDC) National Nosocomial Infection Surveillance (NNIS) System, primary BSIs account for 64% of nosocomial BSIs (2, 4).

"Nosocomial," "community-acquired," "bloodstream infections," and "primary/secondary" are surveillance terms that have stood, essentially unaltered, for almost two decades (4). Yet the health care system has been anything but static during this period. Routine care for patients with serious underlying illnesses and with invasive devices, such as intravascular catheters, has shifted from exclusively acute care settings to nursing homes, rehabilitation centers, free-standing dialysis centers, and homes. Complications of caring for patients with serious illness occur in all of these settings.

In this issue, Friedman and colleagues propose a new classification scheme for BSIs (5). This scheme does not change the fundamental classification of what we call BSIs. It only changes the number of categories of BSIs from two (nosocomial and community-acquired) to three (nosocomial, health care–associated, and community-acquired). Clinicians have recognized that the pathogens and pathogenesis of nosocomial BSIs (for example, those resulting from complications related to placement of an intravenous catheter) and community-acquired BSIs (that is, those not related to a complication from a medical device or procedure) differ. The authors take issue with the term "community-acquired," stating that it is too broad and no longer useful in the new world of serious illness in diverse venues.

The authors reviewed daily microbiology laboratory reports from adults in three hospitals. After excluding patients with contaminated blood cultures, the authors classified patients with BSIs into one of the three new categories. A nosocomial BSI was an infection from patients hospitalized 48 hours or longer. A health care–associated BSI was an infection from a patient who had recent contact with some aspect of health care, such as intravenous therapy via a home health care agency, residence in a nursing home, recent hospitalization, or dialysis. A community-acquired BSI was an infection in a patient with no discernible recent contact with the health care community. After the authors classified the BSIs, they used the CDC definitions to classify whether each patient had a primary or secondary BSI; they then performed a descriptive analysis of the patients.

The authors found that patients with health care–associated BSIs are similar to patients with nosocomial BSIs but different from patients with community-acquired BSIs. On the surface, this distinction seems rather obvious. The invasive devices that might be associated with a BSI in a hospitalized patient are the same as or similar to those used in nonhospitalized patients; in addition, nonhospitalized patients often have the same comorbid factors. The authors' important observation is not that patients with health care–associated BSIs are similar to patients with hospital-acquired BSIs. Rather, it is that they are different from patients with community-acquired BSIs.

The frequency of bacteremia resulting from the use of intravascular devices and from gastrointestinal tract infection was similar in patients with health care–associated and nosocomial BSIs. The frequency of BSIs secondary to urinary tract infection was higher in patients with community-acquired BSIs than in patients with nosocomial and health care–associated BSIs. The pathogens also differed among these groups. *Staphylococcus aureus* was the most frequently isolated pathogen in health care–associated and nosocomial BSIs; *Escherichia coli* and *Streptococcus pneumoniae* were most frequently isolated in community-acquired BSIs. The authors assert that patients with suspected BSIs who have had recent contact with the health care community (health care–associated BSIs) should receive empirical treatment that is similar to the treatment of hospitalized patients with suspected BSIs.

These results should be viewed cautiously. First, the authors studied 504 patients, whereas an estimated 200 000 patients have BSIs annually in the United States. Although some of their findings may not apply to the population as a whole, their basic contribution—the distinction between a health care–associated and a community-acquired BSI—is likely to endure because it reflects fundamental changes in health care. Second, the authors did not measure the risk for health care–associated BSIs. They examined only patients with BSIs (the numerator in a calculation of risk) and did not attempt to determine the size of the population at risk for a health care–associated BSI (the denominator for a risk calculation).

Measuring the risk for BSI can be important for several reasons. It could identify the patients at highest risk for an event so that resources could be used more efficiently for monitoring and intervention. For example, when compared with other hospitalized patients, those patients in critical care areas are disproportionately at risk for BSIs and other nosocomial infections, largely as a result of their exposure to invasive devices (6). Measuring the risk for health care–associated BSI could also be the first step in setting benchmarks of expected performance to avoid BSIs. Benchmarking has resulted in substantial reductions in the rate of BSIs in intensive care units in the NNIS System (7). Benchmarking for health care–associated BSIs, particularly with home health care agencies that provide intravenous therapy in the home, would be an important step toward improving community-based care of serious illness.

Monitoring for BSIs will be more difficult in communities than in hospitals, where it is relatively easy to determine the denominator for a risk calculation. Friedman and colleagues provide some guidance for defining the numerator for a health care–associated BSI rate. However, after patients leave the hospital, data collection for the denominator for a risk calculation becomes exceedingly difficult. An integrated electronic medical record across all venues of health care may eventually solve this problem (8).

As the care of serious illness shifts away from acute care facilities, other complications of care are likely to occur outside the hospital (9, 10). Therefore, the study by Friedman and colleagues should prompt efforts to find other possible adverse events associated with the care of serious illness in the community. Undoubtedly, events such as thrombotic complications, which we have learned to monitor and expect in the hospital setting, are occurring in patients in other settings. Quantifying these events in the community is an attractive target for research.

The study by Friedman and colleagues presents an important clinical message—that clinicians should reconsider therapy for patients with community-acquired BSIs if their recent care falls into the health care–associated category. Empirical treatment with antibiotics that are effective against the commonly isolated *Staphylococcus* species (often with oxacillin resistance) and not only *E. coli* or *Streptococcus pneumoniae*, which are more characteristic of community-acquired BSIs, should be selected. We must change our thinking such that we not only care for serious illness but also look at the setting in which that care is taking place.

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On Being a Patient

Şanti*

He sold Indian vegetables at the local farmers market every weekend. At first glance, he seemed a distinguished older gentleman with a reserved manner and modest attire. The vegetables came from his farm, his refuge from everyday concerns. For the curious, who happened by his truck and inquired about the unusual vegetables so carefully displayed, he would provide a quick recipe. Never a money-making enterprise, the farmer's market represented another teaching venue for him. Every Saturday afternoon, he proudly told his children about the vegetables he sold and the people he met that morning.

His life story is familiar to some. This man grew up in poverty. He was the first in his village to obtain a doctorate degree and go to the United States for further study. By any measure, he was a success. A scientist who thoroughly enjoyed the process of research, he continued to work in the lab, write grants, and supervise graduate students well after he turned 70. He was also a pharmacy professor who had a life-long love for learning and teaching. A medicinal chemist, but not a doctor, he relished telling his children that medical school did not place enough emphasis on therapeutics. Often, they found themselves the preview audience for lectures on pharmacognosy, cancer chemotherapy, and folk medicine that he later gave to students in the school of pharmacy. This gentle man with indefatigable spirit was our father.

It happened during a winter weekend a few years ago. He was admitted to the local university hospital, said to be the best in the area. He had had strange chest sensations for several days. No one, not even his doctor, thought it could be his heart. After all, he still worked full-time in his lab, in the classroom, and on his farm every weekend. For all of his 72 years, he had been able to will illness away. But this time was different. The nagging discomfort would not pass, not with his special peppermint tea, not even with nitroglycerin. He called 911 in the early hours of that Sunday and walked, fully dressed, to the mailbox to meet the rescue squad. "It was a small anterior myocardial infarction," the doctors said, "but he is an excellent bypass candidate."

"You should just be his children and not doctors," we were advised early on. We refrained from looking at his chart or the flow sheets. We looked away as his management was delegated to nurses and physician assistants who did not always know the plan. His surgeons were technically gifted; input from cardiologists and internists was not needed in their unit. The patients were managed according to protocols while the surgeons operated. "Surgical attendings just don't have time to talk to families," the nurses explained, apologetically. This was a system that worked, usually.

Clinical pathways were of little use, 2 days post-op, for the agitated delirium and hypotension that accompanied rapid atrial fibrillation. How do we respond when the surgical fellow, overwhelmed, asks *us* for suggestions? How can we be his children when we are asked to be doctors? Fortune brought to the bedside an experienced surgical attending who ordered life-saving measures. Successfully extubated and weaned from the balloon pump several days later, the patient spoke with his wife and children once again. For a brief moment we felt confident that the battle could be won.

It was not meant to be.

Days later, his condition deteriorated, with falling cardiac output, frequent premature ventricular contractions, and hypoxia. Again agitated, he struggled to convey one last message. "2/20," he scribbled. "Pay the bill, then you can go," he said. "He has ICU psychosis," we reassured our mother. Inside, we worried. The surgical fellow ordered sedation.

We knew it was bad when he coded twice that afternoon. The charge nurse tried to give us hope. "It was lucky that he was in the unit," she said. But how can there be hope when we learn they used open cardiac massage to restart his heart? Harder still, how do we give hope to our mother, or to friends who look to us for words of wisdom and optimism? Yet we did hope, and we waited for the surgeons to talk with our mother. She had never met them and could not understand why they did not speak to her. To this day, she believes they did not care. We waited for words of encouragement from his doctors, but as they passed us in the hallway, they bowed their heads. They too felt helpless, so they avoided us. The nurses' apologies for the doctors' silence did little to ease our concern.

We were determined that he not suffer. His advance directive should have assured that. Our training told us that his prognosis worsened with each hour that he remained comatose. Another resuscitation would be futile, we reasoned. But where do we turn after the attending, in his only conversation with us, explains that he did not believe in "do not resuscitate" orders? Nurses interpret DNR orders as signs of hopelessness, and care will suffer, he asserted. He assured us that his nurses would "know what to do." Why then, did the nurses ask us what they should do if he arrests? "Go slow," we told them. We prayed that they would know what was right.

Two days later, it was clear that our father would not wake up. His mind, the basis of his brilliance, creativity, and curiosity, had been silenced. His eyes, once twinkling

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*In Sanskrit, *Şanti* means "peace"

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with life and a zest for knowledge, were now dull and unseeing. But how do we negotiate a dignified withdrawal of care with an attending who could not communicate with us? We were helped by a physician who cared. Once our professor, now our friend, he was never our father's doctor, yet he became his strongest advocate. With gentle expertise, this kind healer guided us, especially our mother, through this most difficult process.

A week after his cardiac arrest, our father eased our burden. He became hypotensive hours before we had planned to withdraw support. Though he was unresponsive, his breathing, consistent with brain injury, appeared labored. "Keep him comfortable," we pled. The physician-assistant ordered a paralytic agent. Incredulous, we protested the use of a paralytic without sedation, demanding a narcotic instead. His doctors ordered intermittent meperidine without leeway in dose or frequency. As the hours passed, our father lingered, hypotensive and tachypneic. The surgeons did not answer nurses' pages, nor did they come to evaluate. They had moved on to other cases where success was still possible. We were left helpless in our vigil. As the day ended, our friend the advocate, surveying the situation, ordered a morphine drip and weaned the ventilator. The date was 2/20. Our father had found peace.

Our father, the mentor, had taught us a valuable lesson, one seldom taught to doctors: the experience of a patient's family when things go terribly wrong. Here, a physician gifted in humane communication may be as important as one with technical skill. While we were blessed with a physician–friend who could be our father's advocate, we wonder how others would have managed without such connections. We also wonder if things would have been different had the doctors known our father as a person. We wonder if they knew of his remarkable rise from dire poverty in India. We wonder if they knew of the hundreds of pharmacists he had taught or his international reputation as a scientist. We wonder if they knew of his simple dignity and the respect that he showed to all. We wonder if they knew that he was a caring husband and father. We longed for a physician who knew our father as more than just another case.

Time has brought healing and an opportunity for reflection. In addition to the usual sense of profound loss, we were left with the "what ifs" that accompany any bad outcome. As internists, we were tempted to think that, had our father's cardiac arrest occurred in the coronary care unit, the experiences surrounding his ultimate demise might have been different, perhaps better. His preoperative experience, however, suggested otherwise, as communication there appeared to be equally fragmented. As friends and colleagues, physicians and nonphysicians alike, have related personal stories of family illness, we have come to realize that poor communication transcends site of care or physician type. The experiences of others are painfully similar to ours and may be all too common. The underlying message in all is clear: The relationships that clinicians develop (or fail to develop) with their patients and patients' families have an impact that extends beyond the bedside and persists long after the clinical encounter ends.

For us, the impact has extended to our professional lives. We spend more time now speaking with patients and their families. "Patients are people too," we remind housestaff and students. We read journal articles on patient–physician communication and aspire to become students of this emerging art. "We hope that you will teach future generations of surgeons and internists that humanistic qualities are just as much the mark of a qualified physician as technical skill," we wrote to the administration of the medical school. The response was sympathetic, attributing our experience to a "breakdown in communication resulting from a system of faculty coverage intended to maximize the time spent in the operating room by surgical attendings . . . However, this behavior is the exception not the rule, the evidence being the numerous letters the faculty have received over the years commending them for their expert and compassionate care." Action was promised "to decrease the likelihood of such a situation from occurring again." While we had hoped for a more concrete plan for improvement, we have since realized that the problem has no simple solution. Substantive change, the kind that affects more than one institution, will first require recognition by members of the entire profession that a problem exists. Moreover, the frequency with which this situation occurs must motivate the profession to change rather than to accept that little can be done. We must all remember that the next patient in this all-too-common story will also be someone's family member, perhaps even one of our own.

There are lessons in every experience—death, like life, can have purpose and meaning. For us, an important lesson has been the realization that as physicians and family members, we are in a unique position to lobby for change; we have only to seize the opportunity. Our shared experience has engendered in both of us a deep commitment to fostering a dialogue among health professionals on the patient–physician relationship. Recently, at a leading university medical center, we took our first step by participating, as representatives of a patient's family, in a discussion on end-of-life care. Present were faculty and housestaff representatives from internal medicine, surgery, family practice, anesthesiology, and medical education. A distinguished leader in the field had been invited not only to participate in the discussion but also to lend his voice to this effort for the day. The result was a constructive exchange of ideas and personal experiences, and a commitment to finding new ways to teach future clinicians the art of communication. We plan to support and participate in similar activities at other institutions, perhaps someday at the hospital where our father died. By sharing our father's story, we hope to spare other families the agony of reliving our experience. We know that he would have expected nothing less from us.

Rest, dear Father. We are paying the bill.

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Note: The Koppaka Family Foundation was created, in part, to foster a dialogue on the doctor–patient relationship. For more information on the visiting lectureship program, including application procedures, please contact the authors directly by mail or e-mail (koppaka@mindspring.com).

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I felt as if I'd received some sort of blow to the solar plexus. It wasn't physical, but it doubled me over as if it were, and the whole world seemed to go grim and ghastly gray. I sat down on the side of the bed, whimpering like a wounded animal, rocking back and forth in fear and panic.

Inside my chest I became aware of a vast, dark emptiness, in which my heart was being grasped by a huge, cold, steel fist, and slowly squeezed. I was aware of no physical pain, had no sense that I was having a cardiac seizure, a stroke or anything like that; there was only a vast psychic panorama of bleakness, an icy tundra of grayness, and whited skeletons hanging from dead trees, condemned to eternal despair.

Malachy McCourt
Singing My Him Song
New York: HarperCollins; 2000:227-8

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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

LETTERS

COMMENTS AND RESPONSES

Cocaine and Body Temperature Regulation

TO THE EDITOR: We read with interest the article by Crandall and colleagues (1), in which the authors concluded that impaired heat dissipation is a major mechanism by which cocaine elevates body temperature. Although the study objectively demonstrates an increase in body temperature and a reduction in sweat volume, the extrapolation of these results to patients with clinical cocaine toxicity may be unjustified. The small experimental dose of cocaine caused minimal changes in heart rate, mean arterial pressure, and esophageal temperature not reflective of true cocaine poisoning. Moreover, both in patients with cocaine toxicity and in experimental models, it is the psychomotor agitation (notably absent in Crandall and colleagues' patients) that causes hyperthermia (2, 3). Treatment of psychomotor agitation with sedative agents improves both hyperthermia and survival (2, 3).

Although the authors postulate a central mechanism controlling both decreased diaphoresis and cutaneous vascular conductance in the presence of heat stress, this contradicts what is understood about autonomic physiology. Enhanced sympathetic outflow due to cocaine should cause diaphoresis. Cocaine, or benzoylmethylecgonine, is an aminoalcohol tropane derivative that is nearly identical in structure to atropine (4). Could the lack of diaphoresis be due to competitive antimuscarinic effects evident only in the low, noneuphoric doses given to these patients, as is demonstrated in experimental models (5)? These effects may then be overwhelmed by the sympathomimetic effects of cocaine more typical at euphoric doses.

The difference in thermal discomfort between the two groups is interesting. However, since the study used lidocaine as a control, the specific effects of cocaine and lidocaine on the variables tested remain unclear. It is possible that rather than describing a cocaine-induced rightward shift of the perceived temperature versus true temperature curve, the authors have described a leftward shift induced by lidocaine. A lidocaine trial with a true placebo-control arm would help clarify this problem.

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IN RESPONSE: We agree that responses associated with the dose of cocaine administered may be very different from those that occur with cocaine toxicity. However, others have shown that cocaine-induced elevations in core temperature are dose dependent (1, 2). Thus, it is reasonable to suggest that if greater doses of cocaine had been administered, cutaneous vasodilation, sweating, and heat perception may have been even more attenuated. Given that sedating agents decrease internal temperature even in resting healthy persons who do not use cocaine (3), it is not surprising that treatment with sedation agents attenuates the elevation in temperature and improves survival in the cited experimental studies of cocaine toxicity.

We are not proposing that reduced cutaneous vasodilation and sweating is the sole mechanism for elevated internal temperatures due to cocaine use; as indicated in our manuscript, we recognize that increased metabolic activity contributes to elevated internal temperatures. However, our data clearly indicate that in addition to increased metabolism, impaired thermoregulatory responses contribute to the elevation in temperature associated with cocaine use.

Human cutaneous tissue is innervated by a sympathetic adrenergic limb, a sympathetic cholinergic limb leading to sweating, and possibly a sympathetic active vasodilator limb responsible for most of the elevation in skin blood flow during a heat stress (4). Thus, it is far too simplistic to indicate that "enhanced sympathetic outflow should cause diaphoresis." For example, skin-surface cooling causes pronounced increases in skin sympathetic activity but clearly does not cause sweating. If the observed responses were due solely to antimuscarinic effects of cocaine, then only sweating responses would be impaired because local administration of atropine abolishes sweating but does not cause similar alterations in cutaneous vasodilation in humans (5). The observation of similar leftward shifts in the cutaneous vasodilatory and sweating thresholds with cocaine administration therefore strongly suggests that thermoregulatory alterations are central in origin.

We recognize the limitation of using lidocaine as a control solution. However, lidocaine was required to blind the participants, given the anesthetic properties of cocaine. We are unaware of data supporting the contention that lidocaine alters thermoregulatory or perceptual responses during a heat stress. Moreover, one participant in our study also participated in several studies in which similar heat stresses were performed without cocaine or lidocaine. The participant's responses to these heat stresses were virtually identical to those seen in the lidocaine trial but not to those in the cocaine trial.

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Optimal Prediction of Diabetes

TO THE EDITOR: Recent studies demonstrate that it is possible to delay or prevent type 2 diabetes mellitus in persons at high risk for the disease. Proven strategies include weight loss (1–3) through diet and exercise (2, 3) or treatment with metformin (3), or treatment with troglitazone (4), which is no longer commercially available. It is important to identify persons at high risk for type 2 diabetes mellitus.

At issue is how best to identify these at-risk persons. Stern and colleagues (5) advance a "simplified [clinical] model" to estimate a person's risk and contend that it is preferable to performing an oral glucose tolerance test. However, the formula in this clinical model is anything but simple. It requires a programmable calculator or personal computer, as well as the skill to program it. By contrast, the 2-hour oral glucose tolerance test is easy to order and interpret. Furthermore, according to Stern and colleagues' own data, it compares favorably with their clinical model.

The American Diabetes Association has it right when it advocates use of the fasting plasma glucose level and the 2-hour, 75-g oral glucose tolerance test to identify persons at risk for type 2 diabetes mellitus. Far from persuading me to use their clinical model, Stern and colleagues' data convince me that the oral glucose tolerance test is the most straightforward and useful predictor of diabetes risk.

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IN RESPONSE: The Web site www.statcoder.com contains a large collection of physician-support software that can readily be "hot synched" into a personal digital assistant. This Web site was brought to our attention by one of our younger colleagues, who told us that she and others use these programs frequently for patient evaluation and counseling. Among the software programs available on this Web site is the National Cholesterol Education Program Adult Treatment Guidelines III, which includes the Framingham risk equation, an equation analogous to the one presented in our paper. Also available is an equation for estimating preoperative risk. There is no reason why a diabetes risk calculator could not be added to the collection of programs on this or similar Web sites.

It is true that the oral glucose tolerance test is "easy to order," but this is rarely done because of inconvenience and high cost. We recently estimated that the indirect cost attributable to 2 hours of peoples' time would be several billion dollars if widespread screening with the oral glucose tolerance test were implemented in the segment of the U.S. population deemed eligible for screening by the American Diabetes Association (1).

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Prevention of Falls and Injuries in Residential Care

TO THE EDITOR: Some issues arise when trying to interpret the results of Jensen and colleagues' study on prevention of falls and injuries in residential care (1). Although the study had some limitations (effective randomization was not performed, and the "Hawthorne effect" played a role), it is not difficult to assume that the overall intervention worked; most of the measures used were sensible and supported by evidence. However, researchers might want to know which of the strategies or combinations of strategies were efficacious, or at least which were more heavily weighted. Given the study design, it is not possible to determine this. The results could have been caused by too many combinations: a strong effect of the staff education component and no effect of the remaining components, a weak beneficial effect of every individual component, a positive effect of some components (for example, environmental modification and adjusting medications) that makes up for the harmful effect of others (for example, post-fall problem-solving conferences), or a complex synergistic effect among components.

It could be argued that this study focuses not on individual or combinations of components but on the whole program. However, this implies that, for example, a policymaker or a manager of a facility who has faith in the program's effectiveness must "buy the entire pack" or risk something going wrong. In a different setting, some parts of the program may not be able to be implemented because of organizational, economic, or other reasons. Further problems of external validity can easily be imagined. Unless a strong rationale upholds the "unity" of the program, the scientific and practical value of this type of multifactorial trial is limited.

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IN RESPONSE: Given the high-risk target group of residents and the multifactorial nature of falls, the intervention program of our trial combined several measures that targeted known risk factors for falls and fall-related injuries. We agree that with this design it is not possible to determine the specific effect of each measure. However, many interventions in institutional settings have failed to reduce falls (1, 2). This multifactorial fall intervention program was intended to be a first step toward gaining more knowledge about fall and injury prevention in this group of older people at a high risk for falling. A multifactorial approach is in accordance with the pioneering work by Tinetti and colleagues (3) directed at older people living in the community. Even as a first step, the reduction of falls and hip fractures with our program shows that it has value from a human as well as economic point of view. Further subgroup analyses of our study and new studies might elucidate the effect of individual measures.

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RESEARCH LETTER

Severe but Reversible Cholestatic Liver Injury after Pioglitazone Therapy

TO THE EDITOR: *Background:* Pioglitazone, a second-generation thiazolidinedione, is commonly used in the management of type 2 diabetes mellitus. Unlike troglitazone, pioglitazone is generally considered safe from a hepatic standpoint. We know of no reported cases of severe hepatotoxicity resulting from its use.

Objective: To describe a patient with severe cholestatic jaundice possibly due to pioglitazone.

Case Report: A 49-year-old woman with a history of type 2 diabetes mellitus and hypertension was referred to us on 1 August 2000 for evaluation of recent-onset jaundice. Her baseline medications included glipizide, verapamil, and a thiazide diuretic. She had no history of any type of liver disease. On 1 June 2000, the patient began receiving pioglitazone, 30 mg/d. Levels of liver enzymes were unavailable before pioglitazone was started. The patient was seen by an endocrinologist on 23 June 2000. She had no specific symptoms, and laboratory studies showed an aspartate aminotransferase (AST) level of 79 U/L and an alanine aminotransferase (ALT) level of 131 U/L. She continued receiving pioglitazone.

On 14 July 2000, the patient developed jaundice, pale-colored stool, dark urine, itching, pedal edema, and diarrhea. She stopped taking pioglitazone. On 28 July 2000, she was seen by the same endocrinologist for worsening of symptoms; examination showed profound icterus. On 1 August 2000, laboratory studies showed an AST level of 94 U/L, an ALT level of 84 U/L, an alkaline phosphatase level of 6.6 μkat/L, and a total bilirubin level of 368 μmol/L (21.5 mg/dL). Results of tests for hepatitis A, B, and C were negative.

Over the next several days, abdominal imaging (computed tomography and magnetic resonance cholangiography) was performed but failed to reveal any hepatobiliary disease. A liver biopsy showed marked portal edema, a patchy chronic inflammatory cell infiltrate, and marked bile ductular proliferation. The periportal hepatocytes showed a feathery change consistent with cholate stasis. Several interlobular bile ducts showed intraepithelial lymphocytes, evidence of bile duct epithelial damage, regenerative changes, and focal apoptosis. The lobule was largely unremarkable. There was no fibrosis. Results of laboratory tests continued to worsen, and serum bilirubin level peaked at 585 μmol/L (34.2 mg/dL) on 14 August 2000. No specific therapy was provided for severe cholestatic jaundice.

Over the next 8 weeks, symptoms and abnormal results on laboratory tests gradually improved. Six months later, the patient's physical condition was the same as at baseline. Laboratory studies showed an AST level of 26 U/L, an ALT level of 15 IU/L, an alkaline phosphatase level of 2.3 μkat/L, and a total bilirubin level of 7 μmol/L (0.4 mg/dL). At 12-month follow-up, the patient had no symptoms related to liver disease and results of liver chemistries continued to improve.

Discussion: At least two other cases of hepatotoxicity related to pioglitazone have been reported in the literature (1, 2). Maeda (1) described a patient who experienced asymptomatic elevation of serum aminotransferase levels with normal bilirubin levels 7 months after starting pioglitazone therapy. In that patient, elevated levels rapidly normalized after pioglitazone was withdrawn. More recently, May and associates (2) reported a case of mixed hepatocellular–cholestatic liver injury that developed 6 months after pioglitazone was started and normalized within 6 weeks after pioglitazone was withdrawn. In contrast, the reversible liver injury in our patient manifested earlier and was more pronounced.

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BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. Order phone numbers and Web sites can be used to place orders directly with publishers.

Using Information and Communication Technology in Healthcare

Tyrrell S. 176 pages. Oxford, United Kingdom: Radcliffe Medical Pr; 2002. £19.95. ISBN 1857754697. Order at www.radcliffe-oxford.com.

Field of medicine: Computer application.

Format: Softcover book.

Audience: Health practitioners and users of information and communication technology (ICT) in health care.

Purpose: To explain various ICTs in a user-friendly manner, enabling readers to understand and gain confidence to effectively use the technology.

Content: This book explains that the information in health care loses meaning unless it is conveyed in a timely, reliable, and safe manner and that the success of communication technology depends on the manner in which information is presented. The book begins with an explanation of basic purposes and design of computer hardware and the software functioning in it. Databases, the heart of computer systems, are then described; various forms of computer networks, such as LANs, are also discussed in an easy-to-understand manner. The following chapters on data input and output, managing ICT, security, and standards describe more complex technologies. However, they remain concise and informational, providing an understanding of how the technologies are supposed to be applied in a controlled setting. The book closes with a chapter on telemedicine technology, followed by an outlook for technologic development and application in the future.

Highlights: Tyrrell provides many examples to illustrate each point. The book is well structured, is easy to read and understand, and describes highly technical processes without using highly technical jargon. It is both relevant and practical, laying the groundwork for a basic understanding of ICT in health care. If a physician is responsible for installing a computer system and is uncomfortable with the technological jargon, this is an excellent book for closing the comfort gap.

Limitations: The book may contain too much information about the basics of computing for physicians who want immediate access to information about specific systems. Technology changes rapidly—the book is up to date now, but may not be as relevant in the future.

Related reading: Rognehaugh and Rognehaugh's *Healthcare IT Terms* (Healthcare Information and Management Systems Society, 2001) and other books in the Harnessing Health Information Series: Tyrrell's *Using the Internet in Healthcare*, 2nd edition (Radcliffe Medical Pr, 2002); Rigby and colleagues' *Taking Telematics into the 21st Century* (Radcliffe Medical Pr, 2000); and Gillies' *Healthcare Databases: A Simple Guide to Building and Using Them* (Radcliffe Medical Pr, 2002).

Reviewers: Nancy M. Lorenzi, PhD, and Lisa Miller, Informatics Center, Vanderbilt University Medical Center, Nashville, Tennessee.

The Heavenly Ladder

Coulehan J. 64 pages. Canberra, Australia: Ginninderra Pr; 2001. $11.00. ISBN 1740270991. Order at www.ginninderrapress.com.au.

Field of medicine: Poetry.

Format: Softcover book.

Audience: Practicing physicians, medical students, and others in the medical field who want to share the humanity of their patients and discover why most clinicians find so much gratification in their work.

Purpose: To present poetry inspired by clinical experience and reflective encounters with patients and writers.

Content: This slim book contains almost 50 poems divided into four sections. The title and cover art are derived from a Byzantine icon of the heavenly ladder leading to Paradise with a number of would-be saints falling away. I have likened that same icon to academic progress, during which acolytes who do not publish enough perish into perdition. Coulehan, on the other hand, gives words to the perilous climb and the unfulfilled yearning of those who have not done enough to merit salvation—or promotion. The difference between us suggests his optimism and love for most of the world around him.

Highlights: All the poems will comfort the tired physician who wonders why he or she chose clinical practice, for the poems give voice to the emotions that doctors may find hard to express and the longings we cannot always fulfill. The poems are also accessible to physicians unsophisticated in the literary aspects of medicine. The author is a practicing academic physician who finds in his daily medical experience the epiphanies that characterize his poems. He is never sardonic or captious and has always found beauty in his work.

Related reading: Rafael Campo also deals with poetry of daily clinical practice in a mystical and self-revelatory way.

Commentary: The poems present a new strain of sadness, vague discontent, and even a pervasive aura of disappointment, but that lends enchantment.

Reviewer: Howard Spiro, MD, Yale University, New Haven, Connecticut.

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We have often been so swayed by the power of our governing intellectual paradigms that we have found it difficult to take seriously Chinese models that register different orders of experience. Efforts at translation over time have all sought to establish equivalencies between Chinese and western concepts, whether through humors, medical electricity, or, as Kaptchuk's useful article notes, basic scientific evidence. Presumably, other systems are valid only when translatable into biomedical representations of the body.

As those who speak second languages know, each language captures sometimes elusive dimensions of reality. Accurate translation can require retaining original terms, like *qi*. A second language teaches us about our own. The challenge to biomedical researchers involves a willingness to become bilingual, taking both paradigms as expressions of something significant about the real.

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Reference

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IN RESPONSE: Dr. Barnes' comment on the need for a sensitive bilingual encounter between distinct medical systems is greatly appreciated. Indeed, knowledge of other medical systems necessarily encourages self-awareness and is an antidote to arrogance. I find myself so much in agreement with Dr. Barnes that I wonder whether her metaphor of language and "translation" may not be radical enough. The difference between traditional East Asian concepts of medicine and biomedicine extends beyond linguistic issues to the philosophical foundations of their epistemology (1). Chinese medicine relies on the veracity of the senses, the person-centered experience either as reported by the patient or perceived by an observant practitioner. Ultimately, biomedicine depends on deliberately controlled experiments and understands that what is to be most accurate must be shielded from the bias of human observation. More than saying something different about the "real," Chinese medicine and biomedicine engage a reality as distinct and foreign as Ptolemy's cosmos is from Galileo's universe.

Nonetheless, any vibrant medical system needs to do more than sympathetically understand other systems. It may seek to selectively adopt—metabolize, if you will—techniques or strategies independent of theoretical understanding. For example, Chinese medicine incorporated many Greco-Persian herbs during the Tang dynasty (618 to 907 AD) (2), and some practitioners in China are currently in the process of creatively reformulating acupuncture based on modern physiology (3). Indeed, biomedicine has managed to already borrow some of China's traditional medicine without its theoretical underpinning (for example, ephedrine from the Chinese herb *Ephedra sinica* [4] or artemisinin from the Chinese herb *Artemisia apiacea* as a new potential drug for malaria [5]). It may be that a genuine and full medical encounter needs to combine respect and self-reflection with opportunities for creative enrichment.

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RESEARCH LETTERS

Intestinal Pseudo-Obstruction in a Diabetic Man: Role of the Mitochondrial A3243G Mutation

TO THE EDITOR: A 33-year-old Japanese man was referred to our hospital in October 2000 for evaluation of a 4-month history of unexplained abdominal pain and diarrhea, which had already prompted two hospitalizations for intestinal pseudo-obstruction. He had developed diabetes mellitus at 20 years of age and hearing loss at 27 years of age but had no history of seizures or stroke-like episodes. His mother and her brother also had diabetes mellitus. The patient was short in stature (159 cm) and weighed 41 kg.

Physical examination by a neurologist revealed no signs of neuromuscular disease, including diabetic neuropathy, but bilateral sensorineural hearing loss was confirmed. Diabetic retinopathy was not noted. Despite long-term treatment with insulin, the patient's hemoglobin A_{1C} level was 8.7% (normal range, 4.3% to 5.8%). Lactate and pyruvate concentrations, respectively, were 23.5 mg/dL (normal range, 4.0 to 16.0 mg/dL) and 57 μmol/L (normal range, 34 to 102 μmol/L) in blood and 38.9 mg/dL (normal range, 10.0 to 20.0 mg/dL) and 1.2 mg/dL (normal, 0.6 to 1.1 mg/dL) in cerebrospinal

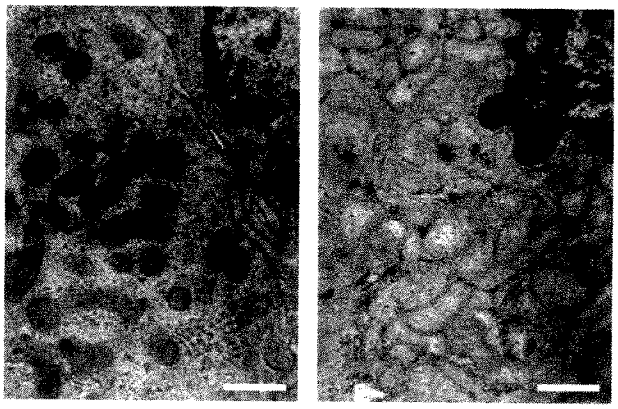

Figure. **Electron micrograph of a mucosal epithelial cell with normal imtochondria (*left*) and a smooth-muscle cell with abnormal mitochondria (*right*).**

Each white bar indicates 500 nm. (Ultrathin sections were double-stained with 1% uranyl acetate and lead citrate; original magnification, ×15 000).

fluid. Findings on colonoscopy were normal, and the result of the xylose absorption test was 8.6 g (normal range, 5.0 to 8.0 g). Histologic examination of a biopsy specimen from the rectum showed no mucosal abnormality.

After the patient's informed consent was obtained, molecular genetic analysis of microdissected tissue revealed the mitochondrial A3243G mutation, which was heteroplasmic (mutant and wild type) in the mucosa and almost homoplasmic (mutant) in the muscularis mucosae. Consistent with these genetic findings, electron microscopy revealed normal mitochondria in the mucosal epithelial cells and an increased number of abnormally swollen mitochondria in the smooth-muscle cells of the muscularis mucosae (**Figure**). The A3243G mutation was also detected in a low percentage of peripheral leukocytes and was confirmed by cloning and DNA sequencing. The patient's abdominal symptoms were somewhat controlled by conventional and conservative therapy.

On the basis of these findings, our patient received a diagnosis of maternally inherited diabetes and deafness (1) that manifested as intestinal pseudo-obstruction because of myogenic, rather than neurogenic, dysfunction caused by the A3243G mutation. The mitochondrial A3243G mutation in transfer $\text{RNA}^{\text{Leu(UUR)}}$ is most commonly associated with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Such a moderately deleterious mutation is usually heteroplasmic in cells that commonly contain hundreds of mitochondria and thousands of mitochondrial DNA; the energy-generating capacity of these cells generally remains near normal until approximately 90% of mitochondrial DNA are mutated (2). Intestinal pseudo-obstruction has been noted in mitochondrial disorders, including MELAS and, most commonly, mitochondrial neurogastrointestinal encephalomyopathy caused by multiple deletions of mitochondrial DNA (3–5). However, the absence of the A3243G mutation in the stomach and intestine of some patients with MELAS and pseudo-obstruction suggests that the primary disease may lie outside the gastrointestinal tract (5). Our study indicates that in patients with mitochondrial disorders, it may be necessary to determine the actual mitochondrial abnormality responsible for specific tissue dysfunction.

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Immune Thrombocytopenia after Losartan Therapy

TO THE EDITOR: An 82-year-old woman presented with nosebleeds and with easy bruising of 2 weeks' duration. She was not bleeding from any other site and had no history of similar symptoms. Other medical conditions included congestive heart failure and depression. Two weeks before presentation, she stopped taking quinapril and was switched to losartan because of cough. Other medications included nortriptyline and bumetanide, which she had been taking for more than 2 years. The patient had no history suggestive of infection; no history of chemotherapy, radiation, or malignancy; and no family history of any bleeding diatheses.

On physical examination, the patient was hemodynamically stable, alert, and oriented and in no acute distress. Results of heart and lung examination were unremarkable. There was no splenomegaly or hepatomegaly. On skin examination, the patient was found to have petechiae over her body and palate. Laboratory evaluation revealed a hemoglobin level of 137 g/L, a leukocyte count of 5.8×10^9 cells/L (40% neutrophils, 47% lymphocytes, 9% monocytes, 3% eosinophils, 1% bands), and a platelet count of 5.0×10^9 cells/L. Flow cytometry of the peripheral blood showed normal CD4–CD8 ratio with no evidence of any lymphoproliferative disorder. A peripheral smear showed decreased platelets without clumping or satellitism.

Because the patient was thought to have immune thrombocytopenia from losartan, this therapy was discontinued. The patient was given one dose of Rh o(D) immune globulin and began receiving oral prednisone, 40 mg/d. Her platelet count improved to 298.0×10^9 cells/L within 1 week. Prednisone was tapered over the next 2 months, and the patient's platelet count has remained normal on follow-up evaluations.

Because thrombocytopenia onset occurred 2 weeks after losartan therapy was started, we believe that our patient had immune thrombocytopenia secondary to this drug. Immune thrombocytopenia secondary to losartan has never, to our knowledge, been reported in the literature. Any future cases would suggest a rare, causal association between losartan therapy and clinically significant thrombocytopenia.

Sreenu Ada, MD
Madhuri Yalamanchili, MD
William Friedenberg, MD
Guthrie/Robert Packer Hospital
Sayre, PA 18840

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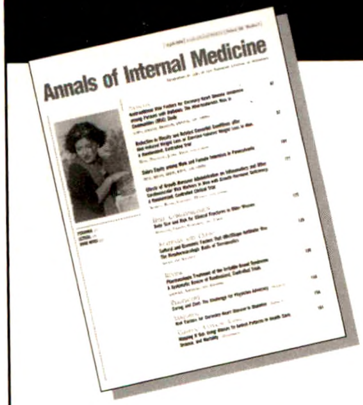

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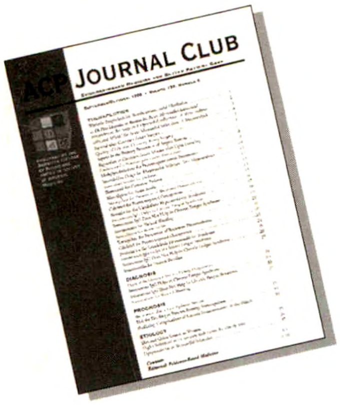

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A 45-year-old woman presents with weight loss of approximately 9 kg (20 lb) over the past 12 months. She has been aware of no change in appetite. She eats three meals daily and snacks most evenings. Her activity has similarly been unchanged. She exercises by walking 2 to 3 miles three or four times weekly. She takes no medication and reports no alcohol or drug use. Review of systems reveals a 1- to 1.5-year history of a pruritic rash on the trunk and extremities. She reports occasional vague abdominal pain and bloating, which subside spontaneously in a few hours, and notes the passage of flatus. She has no food intolerance, difficulty swallowing, sweating, tremor, constipation, diarrhea, or arthritis. She has normal, regular menstrual periods and has two to three stools per day, with no recent change.

The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 ˚C (98.4 ˚F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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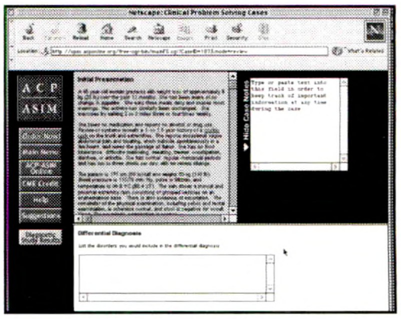

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A.D. Auerbach, R.M. Wachter, P. Katz, J. Showstack, R.B. Baron, and L. Goldman

A voluntary hospitalist service at a community-based teaching hospital had shorter lengths of stay, hospital costs, and mortality than physicians in the control group. The mortality benefit extended beyond hospitalization. Future studies should investigate the ways in which hospitalists increase clinical efficiency and may improve quality of care.

Effects of Physician Experience on Costs and Outcomes on an Academic General Medicine Service: Results of a Trial of Hospitalists 866

D. Meltzer, W.G. Manning, J. Morrison, M.N. Shah, L. Jin, T. Guth, and W. Levinson

Hospitalist care was associated with lower costs and short-term mortality in the second but not the first year of hospitalists' experience. Disease-specific physician experience may be an important determinant of the effectiveness of hospitalists.

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Bone loss accelerates after withdrawal of estrogen therapy but not after withdrawal of alendronate or combination therapy. When managing postmenopausal osteoporosis, clinicians should consider the effects of withdrawing therapy.

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Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer 889

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Effects of Subclinical Thyroid Dysfunction on the Heart 904

B. Biondi, E.A. Palmieri, G. Lombardi, and S. Fazio

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U.S. Preventive Services Task Force

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Screening for Prostate Cancer: An Update of the Evidence for the U.S. Preventive Services Task Force 917

R. Harris and K.N. Lohr

This systematic review supports the U.S. Preventive Services Task Force's position on screening for prostate cancer.

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Implementation of a Voluntary Hospitalist Service at a Community Teaching Hospital: Improved Clinical Efficiency and Patient Outcomes

Andrew D. Auerbach, MD, MPH; Robert M. Wachter, MD; Patricia Katz, PhD; Jonathan Showstack, PhD, MPH; Robert B. Baron, MD, MS; and Lee Goldman, MD, MPH

Background: **Previous investigations of the effect of the hospitalist model on resource use and patient outcomes have focused on academic medical centers or have used short follow-up periods.**

Objective: **To determine the effects of hospitalist care on resource use and patient outcomes and whether these effects change over time.**

Design: **Retrospective cohort study.**

Setting: **Community-based, urban teaching hospital.**

Patients: **5308 patients cared for by community or hospitalist physicians in the 2 years after implementation of a voluntary hospitalist service.**

Measurements: **Length of stay, costs, 10-day readmission rates, use of consultative services, in-hospital mortality rate, and mortality rate at 30 and 60 days.**

Results: **Patients of hospitalists were younger than those of community physicians (65 years vs. 74 years; $P < 0.001$) and were more likely to be of black than of white ethnicity (33.3% vs. 17.9%; $P < 0.001$), have Medicaid insurance (25.1% vs. 10.2%; $P < 0.001$), and receive intensive care (19.9% vs. 15.8%; $P < 0.001$). After adjustment in multivariable models, length of stay and costs were not different in the first year of the study. In year 2, patients of hospitalists had shorter stays (0.61 day shorter; $P = 0.002$) and lower costs ($822 lower; $P = 0.002$). Over the 2 years of this study, patients of hospitalists had lower risk for death in the hospital (adjusted relative hazard, 0.71 [95% CI, 0.54 to 0.93]) and at 30 and 60 days of follow-up.**

Conclusions: **A voluntary hospitalist service at a community-based teaching hospital produced reductions in length of stay and costs that became statistically significant in the second year of use. A mortality benefit extending beyond hospitalization was noted in both years. Future investigations are needed to understand the ways in which hospitalists increase clinical efficiency and appear to improve the quality of care.**

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The organization of inpatient services has been transformed with the development of the hospitalist (1). Traditionally, primary care physicians have cared for their own inpatients. In the hospitalist model, a hospitalist becomes the patient's attending physician during hospitalization and the outpatient physician resumes supervision of the patient after discharge (2).

Several studies have demonstrated improved clinical efficiency in the hospitalist model, but these studies have focused largely on academic centers or health maintenance organizations, or have not used concurrent controls or reported longer periods of follow-up (3–7). One published study examining a hospitalist system at a community-based teaching hospital suggested improvement in clinical efficiency and a reduction in readmissions (8). However, analytic limitations open these findings to many interpretations. To examine the effects of implementation of a hospitalist service on resource utilization and patient outcomes over time, we studied 5308 consecutive patients admitted to an urban community teaching hospital in San Francisco, California.

METHODS

Study Site

Mount Zion Hospital (San Francisco, California) was a 280-bed community-based teaching hospital affiliated with University of California, San Francisco. Mount Zion's inpatient facilities were closed in November 1999 because of financial pressures. During the year before closure, all physicians were aware of the hospital's financial difficulties, but no individual or group was made a focus of efforts to improve clinical efficiency. Discussions about possible closure began 1 month after this study ended, and the hospital closed 5 months later.

Medical patients at Mount Zion Hospital were admitted to one of four medical teams composed of a resident, one to two interns, and zero to three medical students. Mount Zion medical teams cared for common inpatient diagnoses, as well as specialty-associated diagnoses such as cancer, acute myocardial infarction, and cerebrovascular accidents. Housestaff wrote all orders and provided 24-hour coverage to inpatients. Each team had a ward attending physician who before 1 July 1997 was a full-time faculty member serving in this role for 1 month each year. Community-based physicians remained the physician of record for most patients and worked with house officers in the care of their hospitalized patients.

On 1 July 1997, Mount Zion implemented a "voluntary" hospitalist service. Hospitalists, who were University of California, San Francisco, faculty based at Mount Zion, served as ward attendings 6 to 8 months per year and spent their remaining time in ambulatory practice or teaching. Hospitalists cared for patients without primary physicians, patients with faculty or house officer primary care physicians, and patients whose community-based physician chose to use the hospitalist service.

Context

Many studies suggest that hospitalists reduce average length of stay and costs but have little or no effect on patient survival.

Contribution

This 2-year cohort study from a community-based urban teaching hospital found that patients cared for by faculty hospitalists rather than community physicians had shorter lengths of stay, lower costs, and better in-hospital and 1- and 2-month survival rates.

Implications

Length of stay and cost benefits were apparent only in year 2 of the study, which suggests that experience is an important aspect of successful care by hospitalists.

Cautions

The study was retrospective, was done in a single site, and involved only five hospitalists.

–The Editors

Rotating nonhospitalist faculty continued to provide some inpatient care after implementation of the hospitalist service. Patients were admitted to rotating faculty according to the same criteria used for hospitalist services. There were no differences in other inpatient care systems available to community, rotating, or hospitalist physicians (for example, level of housestaff coverage, computer systems, case managers, social workers, or nursing staff).

Patients

Between 1 July 1997 and 30 June 1999, 5907 patients 18 years of age or older were admitted to the medical service at Mount Zion Hospital. We excluded patients who were admitted for chemotherapy or as part of a research protocol ($n = 167$) and those for whom some data on primary diagnosis were missing ($n = 30$). The resulting cohort was composed of 5710 patients, of whom 3693 (65%) were cared for by community-based physicians, 1615 (28%) were cared for by hospitalists, and 402 (7%) were cared for by rotating faculty.

Data Management

At Mount Zion Hospital, data were drawn from TSI (Transition Systems, Inc., Boston, Massachusetts) administrative databases, a cost-accounting system that collects data abstracted from patient charts at discharge. These databases contain information on sociodemographic characteristics, principal diagnosis (in the form of International Classification of Diseases, 9th revision, codes), diagnosis-related group, length of stay, costs, number of consultations, and whether the patient was in an intensive care unit during hospitalization. Data were manually screened for validity of physician designation as hospitalist or community physician by using previously published definitions of hospitalist physician characteristics (1, 2). Discharge summaries of patients who died during hospitalization were examined to validate deaths. An additional 200 discharge summaries of randomly selected patients discharged alive were also reviewed, revealing no errors. Information regarding physician characteristics and board certification was obtained from hospital credentialing databases. Patient survival to points in time after hospitalization was determined by using data from the California State Death Index (for patients admitted before 1 January 1999) and Social Security death indexes (for patients admitted on or after 1 January 1999 and for those who did not reside in California).

Statistical Analysis

To satisfy normality requirements and stabilize variance of residuals, we explored two methods of transforming skewed data on cost and length of stay: logarithmic conversion and truncation at the mean + 3 SDs. Since both techniques yielded similar results, we chose to present results by using truncation, as has been done in previous studies of inpatient costs and utilization (4, 9–11). All costs were adjusted to 1999 U.S. dollars by using an annual inflation rate of 3% (4).

Primary analyses compared 5308 patients cared for by community or hospital-based physicians; we excluded the few patients cared for by rotating physicians from core analyses. This method was chosen to maximize our ability to discern differences in rare outcomes (such as death or readmission), to determine trends in frequent outcomes (such as length of stay), and to maintain focus on our primary question: hospitalist-directed versus community physician–directed inpatient care.

For bivariable comparisons, we used the Fisher exact test or the Wilcoxon rank-sum test. Unadjusted survival rates were estimated by using Kaplan–Meier product-limit methods. We then used multivariable models to determine the independent effect of hospitalist care on patient outcomes. Using automated forward and stepwise selection techniques along with manually entered variables, we fit multivariable linear regression models to determine the independent association of hospitalist care with length of stay and costs. Items were selected on the basis of the statistical significance of their association with the outcome or on observed confounding with other independent variables, or to maintain face validity of the model. Similar methods were used in fitting logistic models of readmission; use of consultations; and Cox proportional hazards models of survival to discharge, 30 days, and 60 days. All analyses were performed by using SAS software, version 8.0 for Windows (SAS Institute, Inc., Cary, North Carolina).

Multivariable models contained adjustment for patient age, sex, ethnicity, insurance type, source of admission (for example, emergency department), site of discharge, whether a cardiovascular procedure was performed during hospitalization, whether the patient received care in an intensive care unit during hospitalization, and case-mix measures. For case-mix measures, specific diagnoses were defined by using International Classification of Diseases, 9th revision, codes for pneumonia, asthma, congestive heart failure, acute myocardial infarction, angina, unstable angina, chest pain, cancer, gastrointestinal hemorrhage, HIV infection, and cerebrovascular accident. Models also contained a variable indexed to admission date to adjust for secular trends. Trends in adjusted outcomes were tested by using variables dummy-coded to indicate service and year of admission.

Because patients were not randomly assigned to hospitalists or community physicians, we performed secondary analyses using a propensity score (12, 13). In our analyses, the propensity score represents the likelihood that any given patient would be admitted to a hospitalist attending physician. The propensity score was calculated in a logistic regression model with attending designation (that is, hospitalist vs. community physician) as the dependent variable. The model contained all covariates in core models, as well as variables found to contribute to nonrandom allocation of patients to specialty care at a P value less than or equal to 0.20. The propensity score was then used in analyses of cost, length of stay, and mortality in two ways: 1) multivariable analyses stratified within tertiles of propensity score and 2) multivariable analyses using the score as a continuous adjustment variable.

RESULTS

Physician Characteristics

One hundred thirteen community physicians, 20 rotating physicians, and 5 hospitalist physicians admitted patients to Mount Zion Hospital during the 2 years of this study. The mean age was 34 years for hospitalists, 40 years for rotating faculty, and 51 years for community-based physicians. All hospitalists were board certified in internal medicine and had graduated from U.S. or Canadian medical schools. Of the rotating faculty, 16 (80%) were board certified and 19 (95%) graduated from U.S. medical schools. Of community-based physicians, 81 (72%) were board certified and 101 (89%) were U.S. graduates.

During these 2 years, community and rotating physicians admitted similar numbers of patients (mean number of admissions per physician, 29 vs. 43; $P = 0.10$). Both community and rotating physicians admitted far fewer patients than did hospitalists, who cared for a mean of 324 patients during the study period ($P < 0.001$ compared with nonhospitalists). Seventy-five (66%) community phy-

Table 1. **Characteristics of Patients Cared for by Community-Based Physicians and Hospitalists at Mount Zion Hospital***

Characteristic	Patients Cared for by Community Physicians (n = 3693)	Patients Cared for by Hospitalists (n = 1615)	P Value†
Median age (10th, 90th percentile), *y*	74 (45, 89)	65 (39, 87)	<0.001
Men, %	1779 (47.8)	755 (46.6)	>0.2
Ethnicity, *n (%)*			<0.001
White	2600 (70.4)	849 (52.6)	
Black	662 (17.9)	537 (33.3)	
Asian	309 (8.4)	149 (9.2)	
Other	130 (3.5)	80 (5.0)	
Insurance type, *n (%)*			<0.001
Capitated	1170 (31.7)	526 (32.6)	
Medicare	2081 (56.4)	623 (38.6)	
Medicaid	377 (10.2)	406 (25.1)	
Private	50 (1.4)	14 (0.9)	
Uninsured	14 (0.4)	43 (2.7)	
Admission source, *n (%)*			
Emergency department	2700 (73.1)	1421 (87.9)	
Referred for admission by physician or clinic	801 (21.7)	115 (7.1)	
Skilled nursing or rehabilitation	79 (2.1)	31 (1.9)	
Transferred from another facility	111 (3.0)	49 (3.0)	<0.001
Discharge disposition, *n (%)*			<0.001
Home	2653 (71.8)	1278 (79.1)	
Skilled nursing or rehabilitation	717 (19.4)	184 (11.4)	
Other facility	58 (1.6)	75 (4.6)	
Dead	265 (7.2)	77 (4.8)	
Intensive care unit stay during hospitalization, *n (%)*	582 (15.8)	321 (19.9)	<0.001
Case mix, *n (%)*			
Acute myocardial infarction	209 (5.7)	85 (5.3)	>0.2
Angina or unstable angina	343 (9.2)	121 (7.5)	0.04
Asthma	84 (2.3)	69 (4.3)	<0.001
Cancer	355 (9.6)	31 (1.9)	<0.001
Chest pain	150 (4.1)	116 (7.2)	<0.001
Gastrointestinal bleeding	74 (2.0)	46 (2.9)	0.06
HIV infection	56 (1.5)	32 (2.0)	>0.2
Pneumonia	240 (6.5)	125 (7.7)	0.10
Cardiovascular procedure during admission (DRG 116, 112, 110)	197 (5.3)	39 (2.4)	<0.001

* Percentages may sum to greater than 100% because of rounding. DRG = diagnosis-related group.

† P value for comparisons of age was based on the Wilcoxon rank-sum test; P values for all other comparisons were based on chi-square tests.

Table 2. **Length of Stay, Cost, Consultation, Readmission, and in-Hospital Death for Patients Cared for by Community-Based Physicians and Hospitalists***

Variable	Patients Cared for by Community Physicians ($n = 3693$)	Patients Cared for by Hospitalists ($n = 1615$)	*P* Value for Unadjusted Difference†	Adjusted Difference, OR, or RH [95% CI]	*P* Value for Adjusted Difference†
Unadjusted median length of stay (10th, 90th percentile), *d*	4.0 (1, 12)	3.0 (1, 11)	<0.001	−0.33 [−0.64 to −0.02]‡	0.03
Unadjusted median costs (10th, 90th percentile), $	4982 (1761, 16 084)	3901 (1474, 14 281)	<0.001	−519 [−930 to −109]‡	0.02
Consultation, *n (%)*					
Patients receiving any consultation	1756 (47.6)	754 (46.7)	>0.2	0.96 [0.84 to 1.09]§	
Patients receiving more than one consultation‖	615 (35.0)	235 (31.2)	0.06	0.85 [0.70 to 1.04]§	
10-day readmission rate, %	191 (5.2)	72 (4.5)	>0.2	0.86 [0.64 to 1.17]§	
Mortality, %					
In-hospital death	264 (7.2)	77 (4.8)	0.03	0.71 [0.54 to 0.93]¶	
Death at 30 days	437 (11.9)	130 (8.1)	<0.001	0.75 [0.61 to 0.92]¶	
Death at 60 days	595 (16.1)	182 (11.3)	<0.001	0.79 [0.66 to 0.94]¶	

* Continuous variables are displayed as median values with the 10th and 90th percentile; categorical variables are displayed as the number and percentage of the total. OR = odds ratio; RH = relative hazard.
† *P* values for comparisons of continuous variables are based on the Wilcoxon rank-sum tests; *P* values for comparisons of categorical variables are based on chi-square tests; *P* values for survival are truncated at discharge, 30 days, and 60 days based on the log-rank test. The referent group for all comparisons is community physicians.
‡ Values given are differences.
§ Values given are ORs among patients of hospitalists.
‖ Among those receiving any consultation.
¶ Values given are RHs among patients of hospitalists.

sicians and 7 (35%) rotating faculty admitted fewer than 24 patients during the study; no hospitalist admitted fewer than 100 patients.

Patient Characteristics and Case Mix

Patients cared for by hospitalists ($n = 1615$) were younger and were more likely to be of black ethnicity than were patients of community physicians ($n = 3693$) (**Table 1**). Hospitalists' patients were more likely to have Medicaid insurance or no insurance and to be admitted from the emergency department rather than a physician's office. They were less likely to be discharged to a nursing home or rehabilitation facility. Patients of hospitalists were more likely to receive care in an intensive care unit during hospitalization.

Patients of hospitalists were more likely to be discharged with a principal diagnosis of pneumonia, asthma, or unspecified chest pain. Patients of community physicians were more likely to have a diagnosis of cancer or angina. No differences in rates of other discharge diagnoses were noted. Community physicians' patients were also more likely to undergo a cardiovascular procedure (coronary angiography or percutaneous transluminal coronary angioplasty).

Comparisons of Patient Outcomes for Each Service

For the entire study (1 July 1997 to 30 June 1999), patients of hospitalists had shorter unadjusted mean lengths of stay (3.0 days vs. 4.0 days; $P < 0.001$) and lower unadjusted hospital costs ($3901 vs. $4982; $P < 0.001$) (**Table 2**). After adjustment in multivariable models, differences in both length of stay (0.33 day shorter; $P = 0.03$) and costs ($505 lower; $P = 0.02$) remained. We noted no differences in unadjusted or adjusted rates of consultation or 10-day readmission rates.

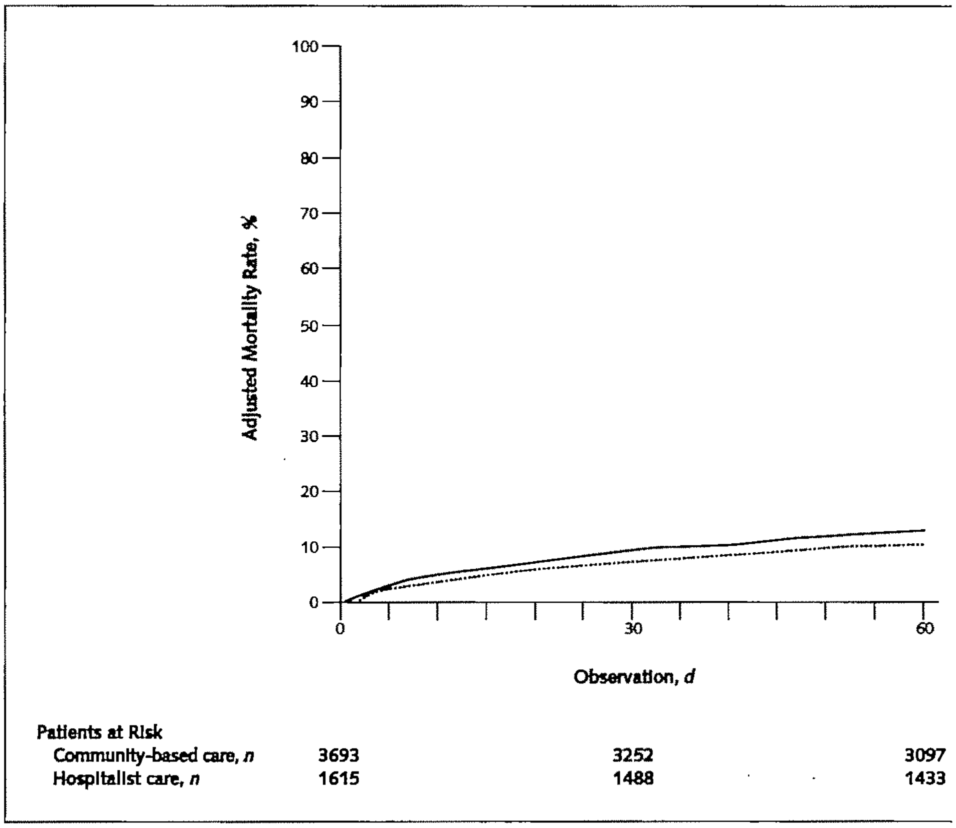
During this study, patients of hospitalists had lower rates of in-hospital death (4.8% vs. 7.2%; $P = 0.03$), corresponding to an unadjusted relative hazard for in-hospital death of 0.75 (95% CI, 0.58 to 0.97) among hospitalist patients. After adjustment in multivariable models, these patients continued to have lower odds of in-hospital death (adjusted relative hazard, 0.71 [CI, 0.54 to 0.93]). This dif-

Table 3. **Trends in Length of Stay and Costs in Years 1 and 2***

Variable	Year 1				
	Patients Cared for by Community Physicians ($n = 1866$)	Patients Cared for by Hospitalists ($n = 735$)	*P* Value for Unadjusted Difference	Adjusted Difference [95% CI]	*P* Value for Adjusted Difference
Unadjusted median length of stay (10th, 90th percentile), *d*	4 (1, 12)	3 (1, 12)	<0.001	0.05†	>0.2
Unadjusted median costs (10th, 90th percentile), $	5020 (1810, 16 022)	4042 (1587, 16 221)	<0.001	21 [−619 to 663]‡	>0.2

* *P* values for unadjusted comparisons of continuous variables are based on Wilcoxon rank-sum tests. The referent group for all comparisons is community physicians.
† $P = 0.002$ for comparison of adjusted length of stay in year 1 and year 2 among patients of hospitalists.
‡ $P = 0.01$ for comparison of adjusted costs in year 1 and year 2 among patients of hospitalists.

Figure. **Adjusted survival of patients admitted to Mount Zion Hospital who were cared for by hospitalists (*dotted line*) and community-based physicians (*solid line*), from Cox proportional hazards models.**



Numbers of patients alive at admission and at 30 and 60 days of follow-up are also displayed. Patients of hospitalists had statistically significantly lower adjusted mortality at both 30 days (2.0% lower; $P = 0.003$) and 60 days (2.6% lower; $P = 0.002$) of follow-up.

ference persisted at 30 and 60 days of follow-up. These relative hazards correspond to an adjusted absolute difference in survival of 2.0% at 30 days and 2.6% at 60 days (Figure), based on conservative estimates derived from the Cox model.

Trends in Length of Stay and Costs

Patients of hospitalists had shorter unadjusted length of stay and lower unadjusted costs in both year 1 (1 July 1997 to 30 June 1998) and year 2 (1 July 1998 to 30 June 1999) (Table 3). After adjustment in multivariable models, differences were not significant in year 1. In year 2, however, we found shorter adjusted length of stay (0.61 day shorter; $P = 0.002$) and lower adjusted costs ($822 lower; $P = 0.002$) among hospitalists' patients. The differences observed in year 2 were entirely due to reduced length of stay and costs in the hospitalist cohort. While no statistically significant change in length of stay (0.24 day shorter in year 2; $P = 0.15$) or costs ($228 lower in year 2; $P > 0.2$) emerged in the community-physician cohort over time, patients of hospitalists showed significant decreases in length of stay (0.77 day shorter in year 2; $P = 0.002$) and

Table 3—**Continued**

Year 2				
Patients Cared for by Community Physicians ($n = 1827$)	**Patients Cared for by Hospitalists ($n = 880$)**	***P* Value for Unadjusted Difference**	**Adjusted Difference [95% CI]**	***P* Value for Adjusted Difference**
4 (1, 12)	3 (1, 10)	<0.001	−0.73 [−1.12, −0.35]†	0.002
4965 (1691, 16 186)	3800 (1226, 13 223)	<0.001	−943 [−1469 to 418]‡	0.002

costs ($818 lower in year 2; $P = 0.01$). There were no statistical differences in adjusted mean length of stay between hospitalists overall or in year-to-year changes, suggesting that no single hospitalist's practice was responsible for the differences observed.

Trends in Consultation, Readmission, and Mortality

We noted no statistically significant trends in consultation over the 2 years of this study. Odds for readmission among patients of hospitalists were lower in year 1 (adjusted odds ratio, 0.72 [CI, 0.45 to 1.17]) than in year 2 (adjusted odds ratio, 0.97 [CI, 0.65 to 1.43]), but this slight increase in odds was not significant ($P = 0.11$). Although confidence intervals are wider because of smaller sample sizes, the adjusted mortality of hospitalist patients was lower at all points of follow-up in both years and was similar to mortality estimates using the entire patient sample. These analyses revealed no within-group trends in patient mortality during the study period.

Comparison of Rotating Faculty to Hospitalist and Community Services

Additional analyses examined the small numbers of patients cared for by rotating faculty. Patients of rotating faculty were similar to those of hospitalists: They were younger, more often uninsured, and more often discharged with a diagnosis of unspecified chest pain than patients of community physicians.

Patients of rotating faculty had unadjusted and adjusted length of stay and costs that were not statistically different from those of patients of hospitalists, overall or in either year. Mortality among rotating physicians' patients was 6.5%, higher than for hospitalists' patients but lower than for patients of community-based physicians. After adjustment, rotating physicians' patients had no differences in relative hazard for in-hospital death.

Secondary Analyses

To explore the durability of our results, we performed many subset and stratified analyses. In models of cost limited to patients 65 years of age and older, hospitalists' patients had a difference in length of stay that was similar in magnitude to that in the entire cohort, although confidence intervals widened because there were fewer patients in this subset (0.33-day difference [CI, −0.76 to 0.06 day]). Similar in-hospital mortality differences were also observed (relative hazard for in-hospital death of hospitalists' patients, 0.66 [CI, 0.48 to 0.91]). When analyses excluded patients with cancer, the difference in length of stay among hospitalists' patients was 0.23 day (CI, −0.55 to 0.10 day); a similar mortality difference was also observed (relative hazard for in-hospital death, 0.79 [CI, 0.60 to 1.05]).

To allow for clustering due to physician-specific effects, we also performed analyses using mixed-effects and generalized estimating models. Analyses adjusting for elements of physician workload (that is, the total number of admissions to each physician during the study period) and specialty training revealed no association with our outcomes of interest, after additional adjustment for independent effects of hospitalist care and case mix.

Finally, we performed analyses accounting for the likelihood of being admitted to a hospitalist physician, limited to patients in the middle tertile of the propensity score. All patients in this group had at least a 30% chance of being admitted to a hospitalist and a 70% chance of being admitted to a community physician. Among the 1878 patients in this middle tertile, the relative hazard was 0.69 (CI, 0.47 to 1.01) for in-hospital death and 0.73 (CI, 0.53 to 1.00) for death at 60 days, point estimates nearly identical to those found in the overall analysis, albeit with wider confidence intervals due to smaller sample sizes.

DISCUSSION

At this community-based teaching hospital, a "voluntary" hospitalist service resulted in reductions in length of stay and cost that became more marked 1 year after implementation. This reduction was due to improved clinical efficiency of hospitalists; efficiency of community physicians did not change. We also observed lower mortality rates among patients cared for by hospitalists both during hospitalization and up to 2 months after discharge.

Previous investigations have consistently demonstrated improved clinical efficiency in hospitalist systems, with no negative effect on patient outcomes (14). To date, no study has noted mortality differences in the hospitalist model (3–7, 14), although one study suggested reduced readmission rates (8). Our findings of improved efficiency over time may provide evidence of growing experience among hospitalists and are similar to those of previous investigations connecting greater volume of cases with better patient outcomes (15–20).

Trends in our cost findings suggest that hospitals should not prematurely judge the value of a hospitalist program. Mount Zion Hospital provided approximately $200 000 annually to support their program. When this amount was added to adjusted cost differences in each year, the program cost the hospital $237 000 in year 1 but saved $500 000 in year 2. However, such analyses, although powerful stimuli for adoption of hospitalist systems (21), do not completely account for its costs and benefits. Complete accounting should include changes in hospital revenues, costs shifted to the outpatient setting, patient and physician satisfaction, and quality-of-care measures more precise than mortality or readmission rates (22).

Because this was an observational study, our findings of lower mortality rates among patients cared for by hospitalists cannot be proven to be causal. The number of in-hospital deaths in our patient cohort was relatively small, and our power to detect differences in these events was limited. Despite many statistical approaches to account for confounding, baseline differences in patient characteristics may partly explain our results. However, our findings are similar to those observed in studies of intensivist management of patients in the intensive care unit, a model with theoretical similarities to the hospitalist model in that both increase the availability of physicians with specific expertise (23, 24). At the very least, our data strongly argue against an excess of deaths among patients of hospitalists, making it highly unlikely that the marked improvements in clinical efficiency came at the expense of quality of care.

This study has several limitations. It remains possible that unmeasured differences in our patient cohorts influenced our results. Our study used administrative data and may be subject to biases inherent in the diagnosis-coding process. However, it seems unlikely that such errors occurred preferentially in either group. Physicians at Mount Zion may have felt pressured to modify their practices and improve clinical efficiency, and such pressures may have changed clinical practice in subtle ways. Nevertheless, both groups of physicians practiced in the same environment, and our findings of stable efficiency and clinical outcome measures in the community physicians' cohort over time indicate that secular trends were not primarily responsible for our results. We also lack information on code status and on whether certain deaths were anticipated (that is, in patients admitted for comfort care). We did not collect cost data beyond hospitalization, but our findings of less frequent discharge to skilled nursing or rehabilitation facilities among patients of hospitalists do not suggest that substantial cost shifting took place (Table 2). Finally, although community-based teaching hospitals are widespread, our results may not apply to other settings.

This study adds to the literature suggesting that the hospitalist model increases efficiency of care for inpatients while maintaining or improving patient outcomes. The precise mechanisms by which the model achieves these improvements remain unclear. Larger studies with random allocation of patients will be required to determine the true effect of hospitalist care on mortality and precise measures of care quality.

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Effects of Physician Experience on Costs and Outcomes on an Academic General Medicine Service: Results of a Trial of Hospitalists

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Background: Hospitalists may decrease costs and improve outcomes in hospitalized patients, but existing evidence is limited and has not identified mechanisms for such effects.

Objective: To study the costs and outcomes for patients on an academic general medicine service assigned to teams led by hospitalists and nonhospitalists.

Design: Cohort study.

Setting: Academic general medicine service.

Patients: 6511 patients admitted to the hospital from July 1997 through June 1999.

Intervention: All patients admitted every fourth day were assigned to 1 of 2 hospitalists caring for inpatients 6 months each year or 1 of 58 nonhospitalists caring for inpatients 1 to 2 months each year.

Measurements: Length of stay; inpatient costs; and 30-, 60-, and 365-day mortality.

Results: Patients assigned to hospitalists (24.8%) and nonhospitalists (75.2%) did not differ in age, race, sex, diagnosis mix, or Charlson index score. In year 1, average adjusted length of stay was 0.29 day shorter for patients cared for by hospitalists than by nonhospitalists (95% CI, −0.66 to 0.06 day; $P = 0.06$); in year 2, average adjusted length of stay was 0.49 day shorter for patients cared for by hospitalists (CI, −0.79 to −0.15 day; $P = 0.01$). Average adjusted costs were not significantly reduced for hospitalists compared with nonhospitalists in year 1 but were reduced by $782 in year 2 (CI, −$1313 to −$187; $P = 0.01$). When years 1 and 2 were combined or when year 1 was analyzed alone, 30-day mortality was not significantly different for hospitalists and nonhospitalists; however, 30-day mortality was 4.2% for hospitalists compared with 6.0% for nonhospitalists in year 2 (CI for difference, 1.8 percentage points [−3.6 to −0.1 percentage points]; $P = 0.04$) and the adjusted relative risk was 0.65 (CI, 0.44 to 0.96; $P = 0.03$). In multivariate analyses, resource use decreased with the physician's cumulative experience in caring for a patient's primary diagnosis. Mortality showed a similar pattern.

Conclusions: Hospitalist care was associated with lower costs and short-term mortality in the second but not the first year of hospitalists' experience. Disease-specific physician experience may reduce resource use and improve patient outcomes; in addition, it may be an important determinant of the effectiveness of hospitalists.

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See related article on pp 859-865 and editorial comment on pp 930-931.

In many countries, patients hospitalized with general medical problems are usually cared for by physicians who specialize in inpatient care (1–3). In the United States, primary care physicians have often served this role historically. However, in recent years, there has been a surge of interest in the care of inpatients by "hospitalists"—physicians who devote at least 25% of their time to the care of hospitalized patients (4).

Key to the growth of hospitalist medicine has been the belief that hospitalists are better suited to contain costs and maintain or improve patient outcomes. Although several recent studies support this belief (5–7), only two had research designs that assigned patients to hospitalists or nonhospitalists without taking into account clinical criteria. Wachter and colleagues showed cost savings but could not demonstrate improved outcomes (5). Moreover, many of the "hospitalist" physicians in that study practiced inpatient medicine for only 1 or 2 months per year. Kearns and colleagues found no effect on either costs or outcomes (8).

These disparate results highlight our limited understanding of the mechanisms by which hospitalists may affect medical care costs or outcomes. Thus, it is difficult to know whether the results of these or other studies are generalizable to other settings. One hypothesis is that the hospitalist's experience in the inpatient setting may be an important determinant of improvements in costs and patient outcomes. Indeed, numerous reports in the literature support a relationship between volume and outcomes for surgeons and some medical specialists (9, 10), but this relationship has never been demonstrated in inpatient general medical care. Benefits of care provided by hospitalists might also result from intrinsic differences in practice style; provision of more focused physician clinical leadership through the development of practice guidelines; or greater emphasis on inpatient care, such as special efforts to see patients on the day of admission. Hospitalists may also have broad effects on practice patterns in the institutions in which they operate by providing a pool of highly experienced inpatient clinicians to whom other physicians (including housestaff) can turn for advice. Understanding the importance of these factors is crucial to the design, evaluation, and improvement of hospitalist programs.

We report the results of a 2-year trial that compared hospitalist care to care by traditional academic internists on the general medicine service at the University of Chicago. In addition to examining the effects of hospitalists on both costs and outcomes, we focused on whether greater overall experience and disease-specific experience with hospitalized patients are important determinants of the effects of hospitalists on costs and patient outcomes.

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Context

Despite the growing number of hospitalist physicians in the United States, evidence about their effect on outcomes of care is limited.

Contribution

This observational study suggests that patients cared for by hospitalists had shorter hospital stays, lower costs, and lower short-term mortality compared with patients cared for by nonhospitalists. These differences became evident only in the second year of the hospitalist program, suggesting that hospitalists' skills improve with additional clinical experience.

Cautions

Because the study included only two hospitalist physicians at one hospital, readers should be cautious about generalizing the findings to other settings.

–The Editors

METHODS

In July 1997, a hospitalist service was established within the general medicine service at the University of Chicago. The goals of the service were to improve the educational environment and contain costs. Two general internists in practice for 2 and 10 years, respectively, agreed to serve as an inpatient attending physician for 6 months of the year, alternating with each other every month between the inpatient service and a shared ambulatory general medicine practice. The 58 nonhospitalist physicians had an average of 9 years of experience after residency (median, 7 years [range, 0 to 34 years]), and 24 had subspecialty training. The hospitalists were not given specific instructions or incentives to alter their practice patterns but were aware that resource utilization, patient outcomes, and housestaff satisfaction were being studied. The hospitalist team alternated in a 4-day call cycle with 3 teams led by traditional academic internists who served as inpatient attending physician 1 or 2 months per year. The 4-day call cycle was arranged so that all patients admitted on each day were assigned to the on-call team (except for the first four patients admitted on weekdays before 5 p.m.). The four excluded patients were assigned to the "short-call" team for that day, which was on day 3 of its call cycle at the time. Thus, all patients were assigned to teams according only to their position in the call cycle, without regard to whether the attending physician was a hospitalist or nonhospitalist.

To minimize hospitalist fatigue, all weekend days on the hospitalist service were covered by the pool of traditional general internists, except when the hospitalist team had been on call the day before. The traditional attending physicians had no weekend days off when they were on-service. Nonhospitalists generally had scheduled ambulatory clinics on weekday afternoons, whereas hospitalists did not have clinic with the expectation that they would be more available to see patients on the day of admission. Attending physicians worked with a single housestaff team in blocks of 2 or 4 weeks. Housestaff and attending physicians were assigned primarily according to requests for which months they would be on-service and without any knowledge of the specific attending physician or housestaff with whom they would be paired. Also, housestaff were assigned to teams so that each house officer had a mix of hospitalist and nonhospitalist attending physicians over the year. Occasionally, a house officer was perceived to require additional oversight; when this occurred (fewer than 3 or 4 of 48 monthly rotations yearly), the residency program director assigned the house officer to an attending physician who she believed might provide better supervision. Housestaff wrote all patient orders. The University of Chicago's Institutional Review Board approved this study.

Study Sample and Data Collection

We studied 6511 patients admitted to the general medicine service from 1 July 1997 through 30 June 1999. Hospital administrative data provided information on age, race, primary and secondary diagnoses, length of stay, and costs. Costs were assessed by using an activity-based accounting system produced by Transitions Systems, Inc. (currently owned by Eclypsis Corp., Delray Beach, Florida). Physician fees were not included. Length of stay was defined as the number of days from when a patient was admitted to the general medicine service to his or her discharge from the hospital, even when the patient was transferred to another service before discharge.

Hospitalized patients were asked to consent to a 15-minute interview to collect detailed health and socioeconomic information and contact information for a follow-up telephone interview 1 month after discharge. We tried to identify proxy respondents for patients unable to complete or consent to the interview. Of the 6511 admitted patients, 4119 (63%) were approached for interviews; 941 (14%) were not approached for interviews because the patient had an admission within the previous 60 days and 1451 (22%) were not approached for interviews because the patient was discharged or had died. Of the 4119 patients approached, 3866 (94%) agreed to be interviewed (including 12% by proxy) and 253 (6%) declined to be interviewed. Similar percentages of patients completed interviews on the hospitalist and nonhospitalist services.

We assessed mortality at 30, 60, and 365 days after admission by linking to the Social Security Death Index (11, 12). A telephone survey of patients or designated proxies who agreed to be interviewed was done at least 1 month after discharge to assess rehospitalization, emergency department use, reported physical function, and patient satisfaction. Of the 3866 patient interviews performed in the hospital, 1-month follow-up surveys were completed for 2768 (72%).

Patient satisfaction with the hospitalization and the care provided by the attending physician was assessed by

Table 1. **Characteristics of Patient and Attending Physician at Admission***

Characteristic	Nonhospitalist Service	Hospitalist Service	*P* Value for Difference
Patients, *n (%)*	4898 (75.2)	1613 (24.8)	
Mean age, *y*	58	58	>0.2
Women, %	61	63	0.11
African-American, %	82	83	>0.2
Diagnosis-related group weight	1.15	1.19	>0.2
Charlson Comorbidity Index score	2.64	2.69	>0.2
Primary diagnosis (ICD-9-CM code), %			
Asthma (493.20, 493.90–493.91)	7.80	7.94	
Pneumonia (486)	6.02	6.08	
Congestive heart failure (428.0)	3.16	3.47	
Urinary tract infection (599.0)	2.78	3.60	
Sickle-cell disease (282.62)	2.89	2.91	
Hypovolemia (276.5)	2.29	2.11	
Cellulitis of the leg (682.6)	2.02	1.80	
COPD (491.21)	1.92	1.36	>0.2
Venous thrombosis (453.8)	1.61	1.55	
Acute pancreatitis (577.0)	1.37	1.05	
Gastrointestinal bleeding (578.9)	1.10	1.55	
Aspiration pneumonitis (507.0)	1.20	1.18	
HIV with opportunistic infection (042)	1.20	0.80	
Systemic lupus erythematosus (710.0)	1.12	0.93	
Hypertensive renal disease with renal failure (403.91)	1.08	0.87	
Other	62.43	62.80	
Weekend admission, %	23	23	>0.2
Attending physicians			
Experience in study period to date, *n cases*	64	410	<0.001
Disease-specific experience in study period to date, *n cases*	2.4	10.1	<0.001
Sees patient on day of admission, %	27	35	<0.001
Weekday admission	27	38	<0.001
Weekend admission	27	24	>0.2

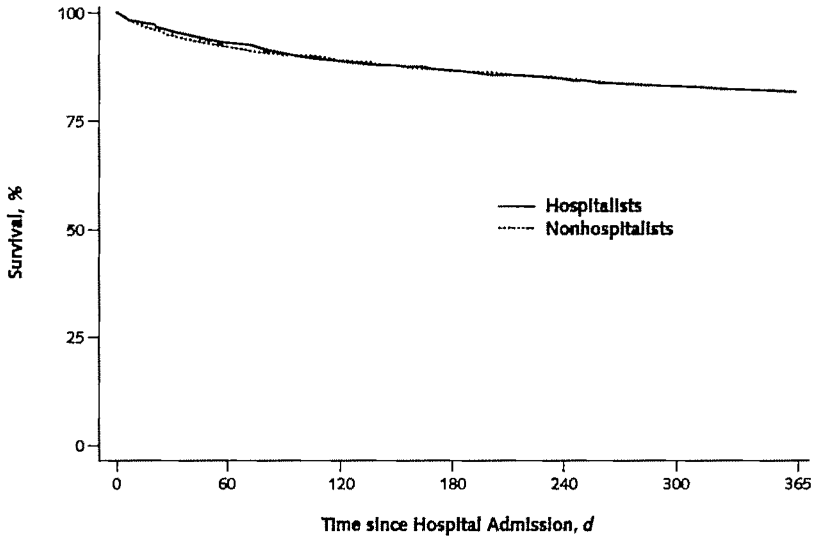
* COPD = chronic obstructive pulmonary disease; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

using questions from the Picker-Commonwealth patient satisfaction survey (13, 14). Health status was assessed by using the self-rated health status and health limitation questions of the Medical Outcomes Study 12-Item Short Form (SF-12) (15). Rehospitalization and emergency department utilization were assessed by respondent recall of all emergency department visits and hospitalizations during the month after discharge (16). We measured case mix by using diagnosis-related group (DRG) weights and measured comorbidity by using a claims-based Charlson Comorbidity Index with a 1-year look-back (17–19). Provider experience was measured by counting the total number of cases and the total number of cases with the same diagnosis (measured by 3-digit International Classification of Diseases,

Table 2. **Length of Stay and Costs**

Variable	Year 1	Year 2	Difference Between Year 2 and Year 1	*P* Value for Difference
Length of stay, *d*				
Nonhospitalists	4.97	4.60	−0.37	0.03
Hospitalists	4.93	4.06	−0.87	0.01
Difference between hospitalists and nonhospitalists	−0.04	−0.54		
P value for difference	>0.2	0.02		
Adjusted length of stay, *d*				
Nonhospitalists	5.03	4.59	−0.44	0.01
Hospitalists	4.74	4.10	−0.64	0.01
Difference between hospitalists and nonhospitalists	−0.29	−0.49		
P value	0.06	0.01		
Total costs, *$*				
Nonhospitalists	8295	8765	470	0.19
Hospitalists	9072	8005	−1067	0.10
Difference between hospitalists and nonhospitalists	777	−760		
P value	0.13	0.13		
Adjusted total costs, *$*				
Nonhospitalists	8701	8801	100	>0.2
Hospitalists	8648	8019	−629	0.05
Difference between hospitalists and nonhospitalists	53	−782		
P value	>0.2	0.01		

Figure. **Kaplan–Meier survival curves for patients cared for by hospitalists and nonhospitalists.**



	0	60	120	180	240	300	365
Patients on hospitalist service, *n*	1613	1501	1435	1392	1363	1334	1311
Patients on nonhospitalist service, *n*	4898	4510	4344	4236	4148	4059	3985

Ninth Revision, Clinical Modification [ICD-9-CM] code) that the attending physician had cared for during the study period up to and including the patient's date of admission.

Statistical Analysis

We used Stata software, version 7.0 (Stata Corp., College Station, Texas), for all statistical analyses. We examined differences in baseline health and demographic characteristics of the patients assigned to hospitalists and nonhospitalists and for differences between hospitalist and nonhospitalist characteristics (such as experience) using *t*-tests for continuous variables and exact binomial tests for binary variables. We tested for differences in length of stay, costs, mortality, emergency department utilization, and readmission by using *t*-tests, with corrections for clustering of patients by attending physician. We used the Pearson chi-square to test for differences in physical function and patient satisfaction. We compared length of stay, costs, and outcomes for the first and second year to assess changes over time.

We also assessed the effects of hospitalists using regression models in which the dependent variables were length of stay, costs, or mortality and the explanatory variables were an indicator variable for hospitalist attending physician, DRG weight of primary diagnosis, Charlson Comorbidity Index score, weekend admission, age in years, ethnicity, and whether the patient was admitted directly to the general medicine service or transferred from another service (transfer status). To account for the non-negativity and skewed distribution of costs and length of stay and to avoid heteroscedasticity in simple least-squares models, we used generalized linear models of length of stay and costs, assuming that the effects of the covariates were proportional (that is, a logarithmic link function) (20, 21). We used the residual diagnostic methods described by Manning and Mullahy (21) to determine that error structure in these generalized linear models was best described by a γ distribution. To address clustering of patients by attending physicians, we did the statistical tests based on robust standard errors (22), with cluster correction for the attending physician. These regression analyses were used to estimate length of stay and costs; we controlled for DRG weight, Charlson Comorbidity Index score, race, age, weekend admission, and transfer status. Statistical tests and confidence intervals for these adjusted values were calculated by using the bootstrap method (23). Logistic regression analyses were done for 30-, 60-, and 365-day mortality. These regressions controlled for DRG weight, Charlson Comorbidity Index score, race, age, weekend admission, and transfer status and included cluster corrections for attending physician.

To explore the mechanism by which hospitalists might affect patient outcomes, we expanded these regression analyses to include overall and disease-specific attending experience during the study period at the time of a patient's admission. The overall experience variable allowed us to test whether costs and outcomes were affected by the attending physician's cumulative experience during the study period, irrespective of diagnosis. The disease-specific experience variable allowed us to test whether the physician's cumulative experience with the patient's diagnosis during

Table 3. **Effects on Mortality**

Variable	Years 1 and 2			Year 1		
	30-Day	**60-Day**	**365-Day**	**30-Day**	**60-Day**	**365-Day**
Unadjusted mortality						
Nonhospitalist, %	5.4	7.9	18.6	4.7	6.9	17.4
Hospitalist, %	4.6	6.9	18.7	5.1	7.1	18.8
Difference (95% CI), *percentage points*	−0.8 (−2.1 to 0.4)	−1.0 (−2.5 to 0.5)	0.1 (−2.1 to 2.3)	0.4 (−1.4 to 2.1)	0.2 (−1.9 to 2.2)	1.4 (−1.7 to 4.5)
P value	0.20	0.21	>0.2	>0.2	>0.2	>0.2
Relative risk (hospitalist vs. nonhospitalist)						
Unadjusted relative risk (95% CI)	0.84 (0.65 to 1.09)	0.87 (0.69 to 1.08)	1.01 (0.87 to 1.16)	1.07 (0.74 to 1.56)	1.02 (0.74 to 1.41)	1.10 (0.89 to 1.36)
P value	0.20	0.21	>0.2	>0.2	>0.2	>0.2
Adjusted relative risk (95% CI)	0.82 (0.62 to 1.08)	0.85 (0.68 to 1.07)	1.00 (0.85 to 1.17)	1.04 (0.70 to 1.55)	0.99 (0.71 to 1.40)	1.09 (0.87 to 1.37)
P value	0.11	0.17	>0.2	>0.2	>0.2	>0.2

the study period affected costs or outcomes. To interpret the estimates of the effects of case counts as the percentage effect of a doubling of experience on the outcome in question, we measured the case count variables as the natural log of the case counts. To avoid possible confounding of the effects of disease-specific physician experience by the effects of diagnoses with many patients, we also included indicator variables for the 60 largest primary diagnoses, as defined according to the 3-digit ICD-9-CM code. To more precisely control for seasonal effects and time trends that could affect both services, we included an indicator variable for each month in the study in these regressions.

Role of the Funding Source

The funding sources played no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

RESULTS

Characteristics of the Hospitalist and Nonhospitalist Services

Of the 6511 patient admissions to the general medicine service, 4898 (75.2%) were assigned to 1 of the 58 nonhospitalists and 1613 (24.8%) to 1 of the 2 hospitalists. Consistent with the assignment of patients to these services in accordance with the call cycle rather than by clinical criteria, patients admitted to these services were very similar in demographic characteristics, mix of primary diagnoses, diagnosis-related group weight, and Charlson Comorbidity Index score (**Table 1**).

Because hospitalists spent more time on the inpatient service over the study, their average overall and disease-specific experience was greater than that of nonhospitalists (**Table 1**). Hospitalists saw 35% of patients on the day of admission, whereas nonhospitalists saw 27%. This difference was the result of the hospitalists' greater likelihood of seeing patients admitted weekdays on the day of admission; hospitalists were not more likely than nonhospitalists to see patients admitted on weekends on the day of admission.

Effects on Length of Stay and Costs

Over the study period, adjusted average length of stay was 4.78 days on the nonhospitalist service and 4.46 days on the hospitalist service (difference, −0.32 day [CI, −0.61 to −0.03 day]; $P = 0.03$). Adjusted average length of stay was reduced by only 0.29 day for hospitalists compared with nonhospitalists in year 1 (CI, −0.66 to 0.06 day; $P = 0.06$), but the difference increased to 0.49 day by year 2 (CI, −0.79 to −0.15 day; $P = 0.01$) (**Table 2**). This difference occurred despite a 0.44-day decrease in adjusted length of stay on the nonhospitalist services between years 1 and 2. The increase in the difference between the hospitalist and nonhospitalist services between year 1 and the difference between them in year 2 was not statistically significant in either of the adjusted analyses (difference, 0.20 day [CI, −0.30 to 0.65 day]; $P = 0.23$) or unadjusted analyses (difference, 0.50 day [CI, −0.11 to 1.08 day]; $P = 0.11$). However, there was a trend toward increasing differences in both analyses.

Over the 2 years, adjusted average costs were $8746 on the nonhospitalist service compared with $8320 on the hospitalist service (difference, −$426 [CI, −$912 to −$31]; $P = 0.03$). As with length of stay, the difference in average costs between the services in year 1 was not statistically significant, but the mean cost for hospitalists was reduced by $782 compared with nonhospitalists in year 2 (CI, −$1313 to −$187; $P = 0.01$). Compared with the pattern for length of stay, the increase in the difference in costs between the hospitalist and nonhospitalist services between years 1 and 2 was more significant in both the adjusted analyses (difference, $729 [CI, −$166 to $1642]; $P = 0.06$) and the unadjusted analyses (difference, $1537 [CI, $126 to $2948; $P = 0.03$).

Effects on Outcomes

Table 3 shows unadjusted and adjusted effects on mortality. Unadjusted analyses show no statistically significant effects on mortality over the 2 years combined, al-

Table 3—**Continued**

Year 2		
30-Day	**60-Day**	**365-Day**
6.0	8.8	19.8
4.2	6.8	18.6
−1.8 (−3.6 to −0.1)	−2.0 (−4.1 to 0.01)	−1.2 (−4.2 to 1.9)
0.04	0.07	>0.2
0.68 (0.47 to 0.98)	0.76 (0.56 to 1.02)	0.93 (0.76 to 1.13)
0.04	0.07	>0.2
0.65 (0.44 to 0.96)	0.74 (0.54 to 1.01)	0.92 (0.74 to 1.14)
0.03	0.06	>0.2

though there are trends toward lower mortality at both 30 and 60 days that are no longer apparent at 365 days. These reductions in short-term mortality are shown graphically through Kaplan–Meier survival curves (Figure). By examining mortality by year, we can see that these findings are the result of the combination of no effect on mortality in the first year but about 2–percentage point decreases in the absolute probability of mortality at 30 and 60 days in the second year that are statistically significant.

Results were similar in the adjusted analyses of mortality. These analyses show trends toward lower mortality for hospitalist service patients at 30 days (adjusted relative risk, 0.82; $P = 0.11$) and 60 days (adjusted relative risk, 0.85; $P = 0.17$) over the 2 years. As in the unadjusted results, the adjusted results reflect the lack of significant effects in year 1 but large and statistically significant effects at 30 days (adjusted relative risk, 0.65; $P = 0.03$) and 60 days (adjusted relative risk, 0.74; $P = 0.06$) in year 2. In-hospital mortality and 30-day readmission, emergency department use, self-reported health status, and patient satisfaction did not differ significantly in either year or over the 2 years combined. However, the trend over the 2 years favored hospitalists in almost all measures (Table 4).

Effects of Experience on Length of Stay, Costs, and Mortality

Table 5 presents the regression analyses of length of stay, costs, and mortality. We used basic models controlling for primary diagnosis with DRG weight and indicator variables for the 60 largest diagnoses, secondary diagnoses with Charlson Comorbidity Index scores, and time trends by using month-specific dummy variables. We found that patients in the hospitalists' services had an 8.0% shorter length of stay, 4.6% lower costs, and a trend toward 18% (relative risk, 0.82) and 14% (relative risk, 0.86) lower relative risk for 30- and 60-day mortality, respectively. Including measures of overall and disease-specific experience eliminates the independent effects of hospitalists. Only the effects of disease-specific experience on resource use are statistically significant; a doubling of previous case volume decreased length of stay by 4.4% and costs by 5.1%. There was also a tendency toward decreased mortality with increasing disease-specific experience, but this decrease was not statistically significant at 30, 60, or 365 days.

DISCUSSION

Our primary conclusions are that hospitalists decreased resource use and short-term mortality and that improvements increased over time in association with disease-specific experience. Although we found more modest differences in year 1 of our study, by year 2, the hospitalists reduced average adjusted length of stay by almost 0.5 day, average adjusted costs by $782, and adjusted mortality at 30 and 60 days by 37% and 28%, respectively. Other outcomes, such as hospital readmission, emergency department visits, and self-reported health status, showed trends toward improvement, although these did not reach statistical significance. Our results provide important evidence to support the use of hospitalists to reduce inpatient resource use while maintaining or even improving outcomes.

Because our findings reflect the experience of a small number of clinicians at one institution, it is important to compare them with the two studies described earlier (Wachter and colleagues; Kearns and colleagues) that examine patients assigned to hospitalists without respect to clinical criteria. Kearns and colleagues compared the use of

Table 4. **Effects on Patient Outcomes**

Service	In-Hospital Mortality Rate (*n* = 6511)*	30-Day Readmission Rate (*n* = 2672)*	30-Day Emergency Department Visit Rate (*n* = 2659)*	30-Day Reported Health Status† (*n* = 2765)	Overall Patient Satisfaction† (*n* = 2689)
	←	*n* (%)	→		
Nonhospitalist	109 (2.2)	245 (12.2)	164 (8.2)	2.73	4.08
Hospitalist	31 (1.9)	71 (10.8)	50 (7.6)	2.78	4.08
Difference in means (95% CI)	−0.3 (−1.1 to 0.5)	−1.4 (−4.2 to 1.4)	−0.6 (−3.0 to 1.8)	0.05 (−0.05 to 0.15)	0.002 (−0.09 to 0.09)
P value‡	>0.2	>0.2	>0.2	0.2	>0.2

* Differences are expressed as percentage points.

† Measured on a scale of 1 to 5; 1 = poor, 5 = excellent.

‡ *t*-test was used for *P* values for in-hospital mortality rate, 30-day readmission rate, and 30-day emergency department visit rate. Chi-square test was used for *P* values for 30-day reported health status and overall patient satisfaction.

new hospitalists with annual hospitalist case volumes similar to those in our study. Of note is the consistency between the lack of resource savings in year 1 in our study and the lack of savings suggested by Kearns and colleagues (8). The resource savings noted in year 2 of our study were similar to the 0.6-day shorter length of stay and $770 reduction in costs found by Wachter and colleagues (5). It is unclear why our initial savings were lower but our later savings were similar to those found by Wachter's team. We suggest two possible explanations for the greater initial savings at the University of California. First, Wachter and colleagues more carefully selected hospitalists for their underlying practice styles. Second, discontinuities of care were present in our system because of the hospitalist weekend coverage system. Although our hospitalist program may not have been as initially effective as the University of California program, our hospitalists were eventually able to achieve similar resource savings. A possible reason for this is that our study lasted 2 years and the University of California study lasted only 1 year. In addition, both of our hospitalists attended 6 months annually, whereas several of the University of California hospitalists attended for less than the 25% minimum proposed definition for hospitalists.

Even more striking than the substantial cost savings in our study are the large and significant reductions in mortality at 30 and 60 days in year 2. Although the increases in survival in our study are present for only a modest period after discharge, they may be important to both patients and their families. To our knowledge, this is the first study without observable differences in the baseline characteristics of patients cared for by hospitalists and nonhospitalists to show statistically significant reductions in mortality. It will be important to confirm these findings in future studies with more patients, clinicians, and institutions. Our results add credence to findings of improved outcomes in a recent nonrandomized study of hospitalists (24).

Because only two hospitalists were involved in our study, questions must be raised about the generalizability of our results. It would be helpful, then, to examine the effects of the individual hospitalists, but the number of patients cared for by each hospitalist was too small to permit a precise estimate of the effects for each hospitalist. This problem is complicated because of the differences between the 2 years and the resulting need to examine each hospitalist separately in each year of the study. In year 1, we found no difference in either resource utilization or mortality for either hospitalist. In year 2, we were still able to see trends toward shorter length of stay, lower costs, and lower mortality for each of the hospitalists; however, these trends did not consistently reach statistical significance by standard criteria. Of note, one of the two hospitalists had a stronger tendency toward lower resource utilization, whereas the other had a stronger tendency toward lower mortality. These findings support the need for future studies with larger numbers of hospitalists.

Our study includes only two hospitalists, but they rapidly accumulated experience leading to substantial variation in overall and disease-specific experience variables. These variables provide insight into mechanisms by which hospitalists may influence outcomes. Resource savings increased over time in relation to disease-specific experience. We also found a trend in which the improvements in mortality over time for hospitalists relative to nonhospitalists were associated with increased disease-specific experience. To the extent that changes in mortality over time are not associated with increased disease-specific experience, it will be important to determine why these changes occurred. One hypothesis is that the hospitalist's overall experience and greater physical presence on the wards led to greater awareness of clinical instability and more timely transfer of unstable patients to the intensive care unit, regardless of clinical diagnosis. Further work should test this and other hypotheses about mechanisms for effect on mortality.

Whether the effects of hospitalists on costs and outcomes is a result of overall or disease-specific experience, our findings suggest that even experienced clinicians, such as our hospitalists, can benefit from greater disease-specific experience. Such "volume–outcomes" relationships for providers have been demonstrated for a wide range of surgical procedures (9, 25, 26) and for treatment of patients with HIV infection in an ambulatory setting (10). However, we believe that our study is the first demonstration of

Table 5. **Multivariate Analysis of Effects on Length of Stay and Costs***

Variable	Length of Stay		Total Costs	
	Basic Model	Model with Experience Variables	Basic Model	Model with Experience Variables
	←		%	→
Hospitalist	−8.0‡ (−12.8 to −3.2)	0.03 (−7.1 to 7.1)	−4.6† (−9.6 to 0.4)	0.1 (−5.9 to 7.8)
Total cases to date		−1.8 (−4.4 to 9.3)		−0.2 (−2.5 to 2.2)
Cases to date with same three-digit ICD-9-CM code		−4.4‡ (−7.8 to −0.9)		−5.1§ (−9.1 to −1.1)

* Percentage effect on outcome variable of hospitalist variable or doubling of experience variables. 95% CIs are given in parentheses. All regressions also include month-specific indicator variables, three-digit ICD-9-CM–specific indicator variables for the primary diagnosis, natural log of diagnosis-related group weight, Charlson Comorbidity Index, patient age, race (African-American vs. other), and indicator variables for weekend admission and whether patient was admitted directly to the general medicine service or transferred to the service from another service. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

† $P < 0.10$.

‡ $P < 0.05$.

§ $P < 0.01$.

this relationship for hospitalized general medicine patients. Moreover, because patients were assigned to attending physicians without consideration of their diagnoses, our findings are not subject to the criticism often made of volume-outcomes relationships—that such associations may occur if providers with lower costs or better outcomes attract larger numbers of patients (9, 25). The volume-outcomes relationship that we observed seems to be a result of the effects of experience on outcomes rather than the reverse.

Given the diversity of diagnoses treated by general internists, our findings about the importance of disease-specific experience highlight many challenges for general internal medicine. These challenges have importance that extends beyond hospitalists. Because no single diagnosis represents more than a small percentage of the admissions treated by general internists, the development of a few critical pathways or practice guidelines is unlikely to be as effective in general internal medicine as it is in specialty practices. If, indeed, patient volume is important, the greater use of hospitalists is one way to increase the experience of physicians caring for hospitalized patients. However, provider experience might also be increased by encouraging clinicians with little inpatient exposure to increase their clinical inpatient work or by focusing general internal medicine practice on fewer diagnoses with greater referral to subspecialists. Our study cannot assess the merits of these options but does suggest the potential value of exploring them and the importance of considering disease-specific experience in evaluating such approaches.

Costs and outcomes improved primarily in the second year of our study, suggesting that hospitalist programs are most likely to be beneficial when staffed by experienced physicians. This is an important concern because the recent rapid growth in the use of hospitalist physicians has created a relative shortage of experienced hospitalists. This problem is compounded by the fact that many hospitalist positions are designed to be transient and staffed by recent residency graduates. Long-term career development paths are unclear. At our medical center, we have addressed this challenge by using some of the financial savings generated by hospitalists to support protected time for promoting the long-term career development of our hospitalists. The hospitalists use this protected time to work on hospital systems improvements and to pursue academic research agendas.

When overall and disease-specific experience are controlled for (Table 5), the direct effects of hospitalists are greatly reduced, suggesting that these factors are largely responsible for the effects of hospitalists. Other factors, such as the selection of physicians with resource-conscious practice styles similar to those of hospitalists and aspects of experience or effort that were not captured by our analyses (such as subspecialty training and years since residency) may also contribute to these effects. The finding that resource savings for hospitalists that existed at the beginning of the study were substantially smaller during the second year suggests that selection of resource-conscious physicians may explain some but not most of our results. Including measures of physician subspecialty training and years since residency in our analyses did not change the effects of experience. Although hospitalists were more likely than nonhospitalists to see patients on the day of admission, this difference decreased from 15% in year 1 to 3% in year 2 ($P = 0.01$ for change in difference), suggesting that greater effort to see the patient on the day of admission does not explain the advantages of hospitalists over nonhospitalists in resource use or outcomes in year 2.

Another possible explanation of the effects of hospitalists is that the hospitalists were more likely to benefit from the development of critical pathways. However, there were only two active pathways on our general medicine service during the study period—for treating pneumonia and for treating deep venous thromboses with low-molecular-weight heparin. Excluding patients with these conditions from our analysis did not substantially alter the findings.

Hospitalists may have also influenced how other clinicians, including housestaff, care for patients. If so, our analysis may underestimate the total benefits of hospitalists. Because we know the assignment of attending physicians to housestaff for each month, it may be possible to track such effects in future analyses. In our analysis, the reduction in length of stay between years 1 and 2 for patients cared for by nonhospitalists may reflect the influence

Table 5—Continued

30-Day Mortality		60-Day Mortality		365-Day Mortality	
Basic Model	Model with Experience Variables	Basic Model	Model with Experience Variables	Basic Model	Model with Experience Variables
←			%		→
0.82 (0.62 to 1.09)	0.96 (0.65 to 1.42)	0.86 (0.68 to 1.09)	0.97 (0.70 to 1.34)	1.01 (0.86 to 1.19)	1.06 (0.84 to 1.32)
	0.95 (0.84 to 1.08)		0.96 (0.86 to 1.07)		1.02 (0.94 to 1.10)
	0.95 (0.75 to 1.19)		0.96 (0.79 to 1.17)		0.92 (0.81 to 1.06)

of hospitalists on housestaff who worked with nonhospitalists. However, the reduction in length of stay could also reflect a secular decline for other reasons. Our estimates of the effects of hospitalists may also underestimate their true effects because house officers perceived to be not as strong as others were occasionally assigned to attending physicians (such as hospitalists) perceived to be stronger.

Because our study is based on a small number of hospitalists at only one institution, it is important to attempt to replicate these findings with more clinicians and institutions. Future studies could help reveal whether physician characteristics, such as subspecialty training, influence costs or outcomes and could further refine understanding of how experience affects costs and outcomes. Moreover, although our findings and those from Wachter and colleagues support the potential for savings by hospitalists in an academic general medicine service, future work should also study hospitalists in community settings. Hospitalists may offer fewer advantages in such settings to the extent that they displace patients' primary care physicians, who might provide better care because of their ongoing relationship with the patient. However, because housestaff are generally not present for 24-hour coverage in community settings, the greater physical presence of hospitalists might be more important in community hospitals than in teaching hospitals.

Finally, although we found statistically significant reductions in mortality at 30 and 60 days and trends toward improvement in almost all other outcome measures, the relative infrequency of adverse outcomes leaves considerable uncertainty about our estimates of effects on outcomes. All previous studies of hospitalists (5–7) have the same limitation, which again indicates the need for larger studies to evaluate the effects of hospitalists.

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Significant Differential Effects of Alendronate, Estrogen, or Combination Therapy on the Rate of Bone Loss after Discontinuation of Treatment of Postmenopausal Osteoporosis

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Combination therapy with alendronate and estrogen for 2 years increases bone mineral density at the spine and hip more than does therapy with either agent alone. Changes in bone mineral density after discontinuation of therapy have not been compared directly.

Objective: To determine the rate of bone loss when therapy with alendronate, estrogen, or both agents is discontinued.

Design: Double-blind, placebo-controlled discontinuation trial.

Setting: 18 U.S. centers.

Patients: 244 postmenopausal, hysterectomized women 44 to 77 years of age.

Intervention: 2 years of therapy with alendronate, 10 mg/d ($n = 92$); conjugated estrogen, 0.625 mg/d ($n = 143$); alendronate and conjugated estrogen ($n = 140$); or placebo ($n = 50$). At year 3, women were allocated into five groups: Twenty-eight women continued to take placebo and 44 women continued to take combination therapy, but 50 women taking alendronate, 81 taking conjugated estrogen, and 41 taking combination therapy were switched to placebo.

Measurements: Bone mineral density and biochemical markers of bone turnover.

Results: Women taking alendronate or combination therapy who were switched to placebo for year 3 of the study maintained bone mass. Bone mineral density in these women was 4.1% (CI, 2.6% to 5.7%) and 6.6% (CI, 5.0% to 8.2%) higher, respectively, at the spine ($P < 0.001$ for both treatment comparisons) and 3.5% (CI, 2.3% to 4.6%) and 3.0% (CI, 1.8% to 4.2%) higher, respectively, at the trochanter ($P < 0.001$ for both treatment comparisons) than that in women previously taking estrogen who were switched to placebo. In contrast, women who were taking estrogen and were switched to placebo during year 3 experienced a 4.5% decrease at the spine (95% CI, −5.0% to −4.0%) and a 2.4% decrease at the trochanter (CI, −2.7% to −2.1%) ($P < 0.001$ for both changes). Compared with women who took placebo for 3 years, women who took estrogen for 2 years and were then switched to placebo had a bone mineral density that was 2.9% higher (CI, 1.2% to 4.6%) at the spine ($P < 0.05$) and 2.9% higher (CI, 1.6% to 4.2%) at the trochanter ($P < 0.001$). Changes in biochemical markers during year 3 did not differ among the groups that discontinued active treatment.

Conclusions: Accelerated bone loss is seen after withdrawal of estrogen therapy but not after withdrawal of alendronate or combination therapy. The differential effects after withdrawal of therapy should be considered in the management of postmenopausal osteoporosis.

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Several antiresorptive agents have been shown to increase bone mass and reduce osteoporotic fractures (1–3). Because greater improvements in bone mass in women using therapy are associated with greater reductions in fracture (4, 5), investigators have begun to examine combinations of antiresorptive therapies to achieve more substantial gains in bone mass. Lindsay and colleagues demonstrated that addition of alendronate to hormone replacement therapy in postmenopausal women resulted in greater increases in bone mass than did maintenance of estrogen therapy alone (6). We previously showed that administration of alendronate and estrogen for 2 years in postmenopausal women with low bone mass resulted in statistically significantly greater increases in bone mass at the lumbar spine and femoral neck than those seen in women taking either agent alone (7). Furthermore, combination therapy was safe and resulted in normal findings on histologic examination of bone.

In clinical practice, a key concern is the potential for accelerated bone loss when antiresorptive therapy is discontinued. Approximately one third of women discontinue hormone replacement therapy within 1 year of initiation (8). Older studies have demonstrated significant losses in bone mass after discontinuation of hormone replacement therapy (9–11). In contrast, when therapy with oral alendronate, 10 mg/d, is discontinued after osteoporosis treatment, bone mass at the hip and spine are maintained for 1 year (12). However, no head-to-head comparison of hormone replacement therapy and alendronate or the combination of antiresorptive therapy after discontinuation has been done. In addition, future losses in bone mass when patients discontinue therapy must be considered in management of osteoporosis in postmenopausal women.

We therefore sought to examine the rate of bone loss after discontinuation of 2 years of alendronate therapy, hormone replacement therapy, or combination therapy. A subset of participants continued to take combination therapy for a third year to determine whether prolonged therapy remained beneficial.

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Context

Alendronate and conjugated estrogen therapy both increase bone mineral density in postmenopausal women, but is the rate of bone loss greater when alendronate or estrogen therapy is discontinued?

Contribution

The discontinuation phase of this double-blind, placebo-controlled trial showed loss of spine and trochanter bone mass in postmenopausal women 1 year after withdrawal of estrogen and no such loss after withdrawal of either alendronate or combination therapy with alendronate and estrogen therapy.

Cautions

The study was not large or long enough to show whether discontinuation of estrogen therapy is associated with more fractures than discontinuation of either alendronate or combination therapy.

–The Editors

METHODS

Study Participants

Four hundred twenty-five postmenopausal women 42 to 82 years of age who had low bone mass were enrolled in a 2-year randomized, double-blind, placebo-controlled clinical trial conducted at 18 centers in the United States (7). Participants were recruited from clinics, private practices, newspaper advertisements, and targeted mailings. All participants who completed the initial study were asked to enroll in the 1-year extension. Participants were told that if they were taking active treatment, they might be randomly allocated to receive placebo or treatment for the third year and that if they were taking placebo, they would continue to do so.

Entry criteria for the initial study are described elsewhere (7). All women had had hysterectomy and had a bone mineral density at the lumbar spine that was less than or equal to a T score of −2.0 SDs below the peak bone mass in young adults. Data on presence or absence of ovaries were not collected. Exclusion criteria were metabolic bone disease, a low serum 25-hydroxyvitamin D level, use of medications known to affect bone turnover, renal insufficiency, severe cardiac disease, and recent major upper gastrointestinal disease.

The institutional review board at each clinical site approved the extension protocol. After signing the extension consent form and undergoing baseline evaluation for the extension, participants were allocated to blinded treatment on the basis of their original treatment in the first 2 years of the study. The randomization process was centrally determined by a statistician; as in the initial study, treatment allocation was concealed.

Design

As described for the initial study at each center, patients were randomly allocated to one of four treatment groups: placebo ($n = 50$); alendronate, 10 mg/d ($n = 92$); conjugated estrogen, 0.625 mg/d ($n = 143$); or alendronate, 10 mg/d, plus conjugated estrogen, 0.625 mg/d ($n = 140$) (**Figure 1**). The conjugated estrogen used was Premarin (Wyeth-Ayerst, Philadelphia, Pennsylvania). All women received calcium carbonate to provide 500 mg of elemental calcium daily.

At the end of the second year, 244 of the 425 women (57%) continued in a 1-year extension of the study (**Figure 1**). Of these women, 28 who previously received placebo continued to do so. Women who were taking combination therapy were reallocated to continue taking combination therapy ($n = 44$) or switch to placebo ($n = 41$). In addition, 50 participants taking alendronate alone and 81 participants taking conjugated estrogen alone for the first 2 years were assigned to placebo for the third year. All patients and investigators remained blinded to medication allocation. Patients continued to receive calcium supplementation during the third year.

Outcome Measures

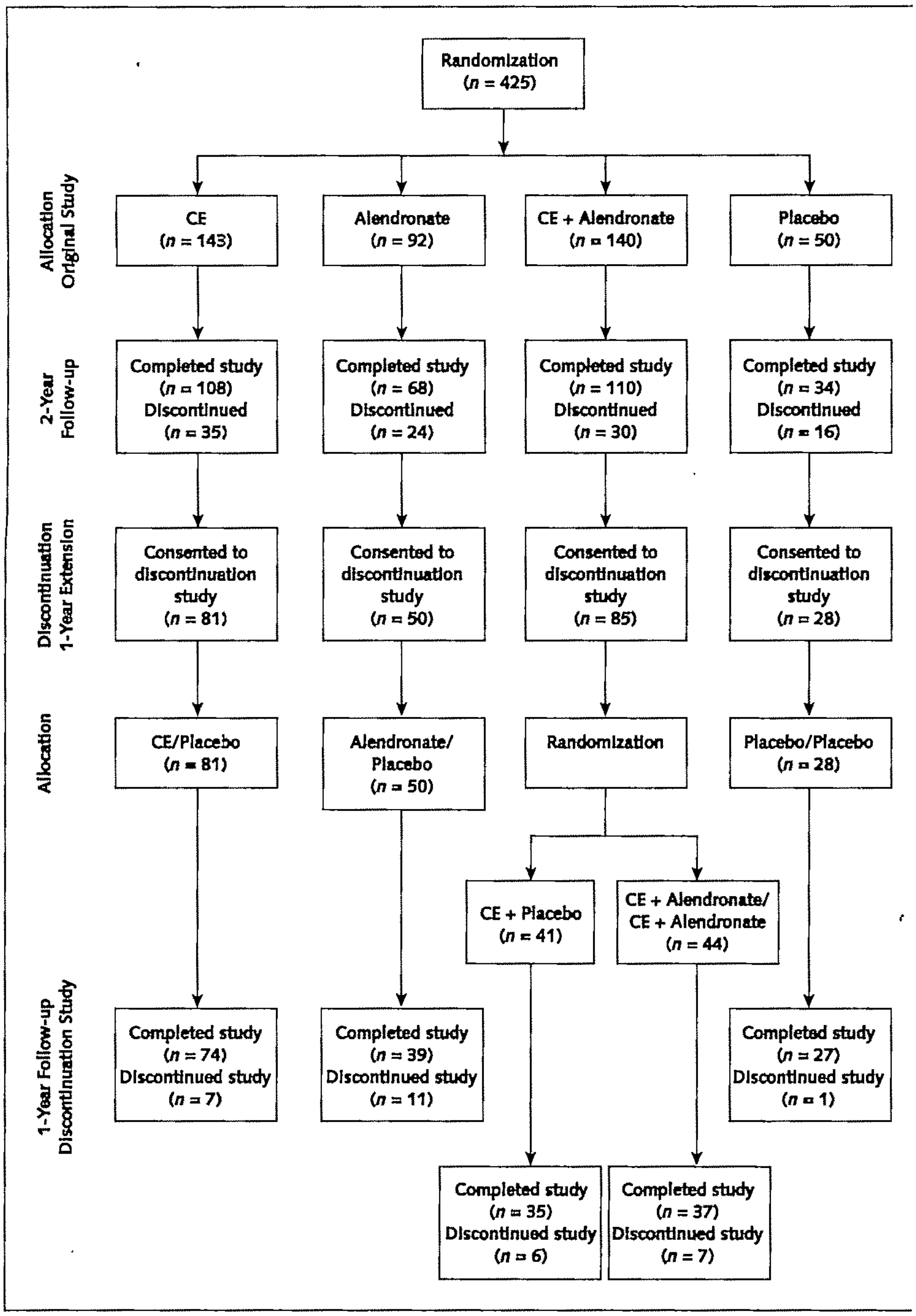
Women were examined at month 24 (baseline of the 1-year extension), month 30, and month 36. Bone mineral density of the lumbar spine, hip (femoral neck, trochanter, total hip), and total body were assessed by using dual-energy x-ray absorptiometry with QDR-1000W, QDR-1500, or QDR-2000 series bone densitometers (Hologic, Inc., Bedford, Massachusetts). A standard phantom was used for cross-calibration at all sites. Serum and urine samples were also obtained at months 24, 30, and 36 for assessment of biochemical markers of bone turnover, namely bone-specific alkaline phosphatase and urinary *N*-telopeptide cross-links of collagen type I, corrected for creatinine.

Statistical Analysis

We used SAS software, version 6.12, TSLevel 0060, PROCedureGLM (SAS Institute, Inc., Cary, North Carolina) to analyze the data. The primary efficacy end point was the mean difference between groups in the percentage change in bone mineral density at the lumbar spine from month 24 to month 36. Secondary efficacy end points were the mean percentage changes in bone mineral density of the hip and total body and biochemical markers of bone turnover. Overall percentage changes from month 0 to 36 in spine, hip, and total-body bone mineral density were also analyzed.

The prespecified analysis was based on an intention-to-treat approach. At study design, we prespecified that all patients who had a baseline measurement and at least one measurement during treatment would be included in the analysis according to the group to which they were randomly allocated. The missing data were approximated by carrying forward the last available value on treatment forward to the missing time point. No data from the original

Figure 1. **Design of original 2-year study and reallocation to extension phase for year 3.**


Randomization (*n* = 425)
Allocation Original Study
CE (*n* = 143)
Alendronate (*n* = 92)
CE + Alendronate (*n* = 140)
Placebo (*n* = 50)
2-Year Follow-up
Completed study (*n* = 108) Discontinued (*n* = 35)
Completed study (*n* = 68) Discontinued (*n* = 24)
Completed study (*n* = 110) Discontinued (*n* = 30)
Completed study (*n* = 34) Discontinued (*n* = 16)
Discontinuation 1-Year Extension
Consented to discontinuation study (*n* = 81)
Consented to discontinuation study (*n* = 50)
Consented to discontinuation study (*n* = 85)
Consented to discontinuation study (*n* = 28)
Allocation
CE/Placebo (*n* = 81)
Alendronate/ Placebo (*n* = 50)
Randomization
Placebo/Placebo (*n* = 28)
CE + Placebo (*n* = 41)
CE + Alendronate/ CE + Alendronate (*n* = 44)
1-Year Follow-up Discontinuation Study
Completed study (*n* = 74) Discontinued study (*n* = 7)
Completed study (*n* = 39) Discontinued study (*n* = 11)
Completed study (*n* = 27) Discontinued study (*n* = 1)
Completed study (*n* = 35) Discontinued study (*n* = 6)
Completed study (*n* = 37) Discontinued study (*n* = 7)

CE = conjugated estrogen.

2-year study were carried forward to the extension period for any assessment of change. Women who violated the protocol were excluded from analysis of biochemical markers, as previously reported (7).

Between-group comparisons of bone mineral density and biochemical measures were made by using analysis of variance techniques, with treatment, center, and treatment-by-center as factors. The assumption of homoscedasticity for the analysis of variance model was assessed by using the Levene test, and the normality assumption was assessed by using the Shapiro–Wilk test (13). If the assumptions were violated, a nonparametric method was used to corroborate the parametric results. The Fisher exact test was used to compare treatment groups for the proportion of participants who exceeded predefined limits of change in laboratory safety variables (13). Power calculations based on estimated sample sizes of 56 and 84 participants in the alendronate/placebo and estrogen/placebo treatment groups, respectively, yielded an estimate of 92% power to detect a 1.5% difference between mean percentage changes from

Table 1. **Baseline Characteristics of Participants in the Extension Study***

Variable	Placebo/Placebo Group ($n = 28$)	Alendronate/Placebo Group ($n = 50$)	Estrogen/Placebo Group ($n = 81$)	Combination Therapy/ Combination Therapy Group ($n = 44$)	Combination Therapy/ Placebo Group ($n = 41$)
Age, *y*	64 ± 9	63 ± 8	62 ± 8	65 ± 7	64 ± 8
Time since menopause, *y*	26 ± 11	24 ± 7	22 ± 9	25 ± 10	22 ± 9
White ethnicity, %	86	88	86	89	95
Smoking, %	11	8	15	18	10
Alcohol consumption, %	7	10	7	11	10
Height, *mm*	1589 ± 58	1593 ± 66	1597 ± 64	1594 ± 69	1615 ± 51
Body mass index, *kg/m²*	30.0 ± 7.1	25.8 ± 4.3	26.6 ± 5.4	26.9 ± 3.8	26.7 ± 4.6
Daily calcium intake, *mg*	1457 ± 552	1300 ± 488	1273 ± 424	1343 ± 1200	1200 ± 414
Bone mineral density, *g/cm²*					
Lumbar spine	0.76 ± 0.09	0.83 ± 0.07	0.80 ± 0.08	0.83 ± 0.08	0.85 ± 0.07
Femoral neck	0.66 ± 0.11	0.64 ± 0.08	0.65 ± 0.09	0.66 ± 0.08	0.67 ± 0.10
Total hip	0.76 ± 0.09	0.78 ± 0.10	0.80 ± 0.08	0.83 ± 0.08	0.85 ± 0.07
Urinary *N*-telopeptide cross-linked collagen type 1 level, *nmol BCE/mmol creatinine*	49.3 ± 23.0	19.8 ± 8.8	26.0 ± 14.5	13.6 ± 8.1	13.8 ± 5.3
Serum bone-specific alkaline phosphatase level, *ng/mL*	12.7 ± 5.2	7.1 ± 2.0	8.0 ± 4.2	5.4 ± 1.8	6.0 ± 2.2
Serum calcium level, *mmol/L (mg/dL)*	2.28 ± 0.1 (9.1 ± 0.4)	2.30 ± 0.13 (9.2 ± 0.5)	2.28 ± 0.1 (9.1 ± 0.4)	2.28 ± 0.1 (9.1 ± 0.4)	2.25 ± 0.1 (9.0 ± 0.4)
Serum phosphate level, *mmol/L (mg/dL)*	1.16 ± 0.16 (3.6 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.10 ± 0.16 (3.4 ± 0.5)	1.07 ± 0.13 (3.3 ± 0.4)

* Unless otherwise indicated, data are presented as the mean ± SD.

month 24 to month 36 in bone mineral density at the lumbar spine ($\alpha = 0.05$, two-tailed test).

As requested by the journal editors, data on bone mineral density were also analyzed by using a mixed-model analysis, and results of this analysis are presented. An appropriate curvilinear function was fitted to the actual data, and the function was estimated by using all data available across time points for each participant. A model that regressed bone mineral density versus log (month + 1) provided the appropriate fit for the 3-year data and was used to analyze these data. The variable log (month + 1) was used because log (month) is undefined when month is 0, and log (month + 1) yields the value 0 at baseline. The fitted values from the model were used to obtain the percentage change during the period of interest. Data on bone mineral density from the mixed-model analyses are presented unless otherwise specified.

Role of the Funding Source

Data were collected by investigators at each study site with the support of Merck Research Laboratories, Rahway, New Jersey. Analyses were performed by statisticians at Merck & Co., Inc. Data were interpreted by the authors, who submitted the manuscript for publication.

RESULTS

Patient Characteristics and Retention

Baseline randomization characteristics did not differ between participants who entered the extension phase and those who did not. Baseline demographic characteristics of the 244 women who entered the extension phase were similar in all treatment groups (**Table 1**). Two hundred twelve women completed the extension phase, including 39 in the alendronate/placebo group, 74 in the conjugated estrogen/placebo group, 35 in the combination therapy/placebo group, 27 in the placebo/placebo group, and 37 in the combination therapy/combination therapy group (**Figure 1**). In the active treatment group, compliance (defined as taking the study drug for at least 75% of the time spent in the study) was 100%. No compliance data were collected for calcium supplementation.

Bone Mineral Density and Markers of Bone Turnover

During the extension period, women who received estrogen during the first 2 years and were then switched to placebo showed significant losses in bone mineral density at the spine (−4.5% [95% CI, −5.0% to −4.0%]), total hip (−1.8% [CI, −2.1% to −1.6%]), femoral neck (−2.4% [CI, −2.7% to −2.2%), and trochanter (−2.4% [CI, −2.7% to −2.1]) (all $P < 0.001$) (**Figures 2 and 3**). Patients in the alendronate/placebo or combination/placebo group showed no significant change in bone mineral density at any of the skeletal sites studied. During the third year, the difference in bone mineral density between women in the alendronate/placebo group and those in the estrogen/placebo group was 3.5% (CI, 2.6% to 4.3%) at the spine, 2.5% (CI, 2.0% to 3.0%) at the trochanter, 2.0% (CI, 1.5% to 2.4%) at the total hip, and 2.1% (CI, 1.7% to 2.5%) at the femoral neck. Compared with the placebo/placebo group, women in the estrogen/placebo group had losses in bone mineral density of 4.4% (CI, −5.3% to −3.4%) at the spine and 2.4% (CI, −3.0% to −1.8%) at the trochanter. No significant differences in bone mass at the spine or hip were observed between the alendronate/placebo group and the placebo/placebo group, the combination therapy/placebo group and the placebo/placebo group, or the combination therapy/combination therapy group and the placebo/placebo group.

Analyses using the last value carried forward provided similar results. For example, the difference in bone mineral density between women in the alendronate/placebo group versus the estrogen/placebo group was 3.6% at the spine (CI, 2.4% to 4.8%), 2.5% at the trochanter (CI, 1.2% to 3.7%), 1.9% at the total hip (CI, 0.9% to 3.0%), and 2.2% at the femoral neck (CI, 0.7% to 3.6%).

During the extension phase, levels of urinary *N*-telopeptide cross-links of collagen type I did not change significantly in the placebo/placebo group or combination therapy/combination therapy group but increased significantly in the estrogen/placebo group (increase, 66.1% [CI, 48.3% to 85.9%]), alendronate/placebo group (72.3% [CI, 48.2% to 100.3%]), and combination/placebo group (84.4% [CI, 57.6% to 115.8%]) (all $P < 0.001$) (**Figure 4**). The increases in urinary *N*-telopeptide cross-links of collagen type I levels in patients who discontinued active treatment did not differ among groups. However, an 83.8% difference (CI, 54.2% to 113.5%) was observed between the alendronate/placebo group and the placebo/placebo group, and an 80.4% difference (CI, 56.8% to 104.0%) was observed between the estrogen/placebo group and the placebo/placebo group.

Serum levels of bone-specific alkaline phosphatase increased significantly in the placebo/placebo group (17.2% [CI, 4.1% to 32.1%]; $P = 0.005$), estrogen/placebo group (66.5% [CI, 54.5% to 79.5]); $P < 0.001$), alendronate/placebo group (58.2% [CI, 42.8% to 75.2%]; $P < 0.001$), combination therapy/placebo group (66.3% [CI, 45.9% to 85.0%]; $P < 0.001$), and combination therapy/combination therapy group (21.1% [CI, 9.2% to 34.3]; $P < 0.001$) (**Figure 4**). The increases in serum levels of bone-specific alkaline phosphatase in the estrogen/placebo, alendronate/placebo, and combination therapy/placebo groups were significantly greater than those observed in the placebo/placebo group (differences of 40.1% to 51.7%; all $P < 0.001$) but did not differ significantly.

At the conclusion of the study (3 years), women treated with alendronate or combination therapy for 2 years who were then switched to placebo showed significant increases in bone mineral density of the spine (6.0% [CI, 4.7% to 7.3%] and 8.5% [CI, 7.1% to 9.8%], respectively; both $P < 0.001$); the net difference between the two groups was 2.5 percentage points (CI, 0.7 to 4.3 percentage points). Women who received estrogen for 2 years and were then switched to placebo had a significant change of 1.9% (CI, 1.0% to 2.8%) in bone mineral density of the spine over 3 years; the net difference compared with the placebo group was 2.9% (CI, 1.1% to 4.6%). At 3 years, bone mineral density of the spine in the alendronate/placebo group was 4.1% (CI, 2.6% to 5.6%) higher than that in the estrogen/placebo group. Bone mass at the spine in women who took combination therapy for all 3 years was 11.2% higher (CI, 9.2% to 13.2%) than that in the placebo group.

Similar results were obtained with last-value-carried-forward analyses. After 3 years of treatment, bone mass at the spine was 4.4% higher (CI, 2.8% to 6.0%) in the alendronate/placebo group than in the estrogen/placebo group and 11.4% higher (CI, 9.3% to 13.5%) in the combination therapy group than in the placebo group.

Women treated with alendronate/placebo or combination therapy/placebo showed significant increases in bone mineral density at the total hip (4.5% [CI, 3.9% to 5.2%] and 4.4% [CI, 3.7% to 5.0%], respectively) at 3 years (both $P < 0.001$). Over 3 years, total-hip bone mineral density increased significantly by 2.6% (CI, 2.1% to 3.0%) in women treated with estrogen/placebo; the net change was similar to that in the placebo group. By comparison, total-hip bone mineral density was 4.0% higher (CI, 3.0% to 5.0%) in the alendronate/placebo group than the placebo/placebo group. Women who took combination therapy for all 3 years had a total-hip bone mineral density that was 6.4% higher (CI, 5.4% to 7.5%) than that in the placebo/placebo group. Similar trends were noted at the femoral neck. Compared with the estrogen/placebo group, bone mineral density at the trochanter was 3.4% higher (CI, 2.3% to 4.6%) in the alendronate/placebo group and 3.0% higher (CI, 1.8% to 4.2%) in the combination therapy/placebo group.

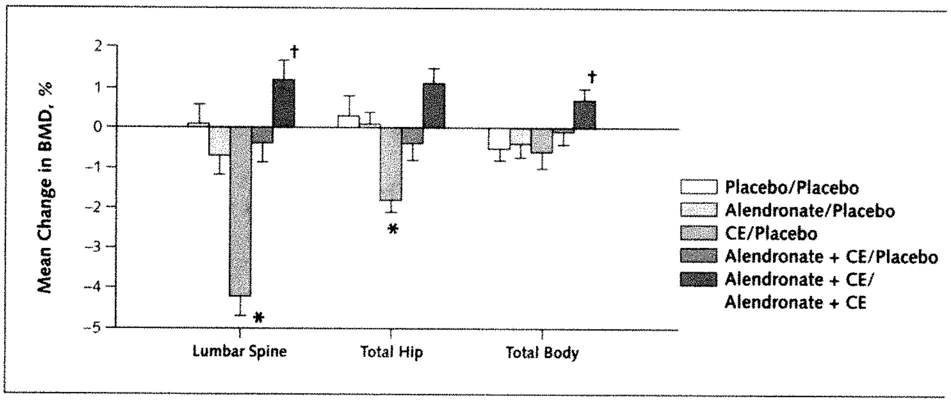
Few differences among groups were noted for total-body bone mineral density at 3 years. However, total-body

Table 2. **Between-Treatment Differences at 36 Months***

Between-Treatment Comparison	Mean Difference in Bone Mineral Density (95% CI), %		
	Lumbar Spine	Trochanter	Total Hip
Alendronate/placebo group vs. placebo/placebo group	7.0 (5.0 to 8.9)	6.4 (4.9 to 7.9)	4.0 (3.0 to 5.0)
Estrogen/placebo group vs. placebo/placebo group	2.9 (1.2 to 4.6)	2.9 (1.6 to 4.3)	2.1 (1.2 to 3.0)
Combination therapy/placebo group vs. placebo/placebo group	9.5 (7.4 to 11.5)	5.9 (4.4 to 7.4)	3.9 (2.9 to 4.9)
Combination therapy/combination therapy group vs. placebo/placebo group	11.2 (9.3 to 13.2)	9.1 (7.6 to 10.6)	6.5 (5.4 to 7.5)
Alendronate/placebo group vs. estrogen/placebo group	4.1 (2.6 to 5.6)	3.4 (2.3 to 4.6)	1.9 (1.1 to 2.7)
Combination therapy/placebo group vs. alendronate/placebo group	2.5 (0.7 to 4.3)	−0.4 (−1.8 to 0.9)	−0.1 (−1.1 to 0.8)
Combination therapy/placebo group vs. estrogen/placebo group	6.6 (5.0 to 8.2)	3.0 (1.8 to 4.2)	1.8 (1.0 to 2.6)

* Mixed-models analysis.

Figure 2. **Mean (±SE) percentage change from year 2 to year 3 in bone mineral density (*BMD*) at the lumbar spine, total hip, and total body.**



Vertical lines represent SEs. *$P \le 0.001$; †$P \le 0.01$. CE = conjugated estrogen.

bone mineral density was 2.8% (CI, 2.3% to 3.3%) higher in the combination therapy/combination therapy group than in the placebo/placebo group. Last-value-carried-forward analyses provided similar results.

Over 3 years, urinary levels of *N*-telopeptide cross-links of collagen type I did not change significantly in the placebo/placebo group but decreased significantly in the estrogen/placebo group (−15% [CI, −24.7% to −4.1%]; $P =$ 0.005), alendronate/placebo group (−38.6% [CI, −47.8% to −27.7%]; $P <$ 0.001), combination therapy/placebo group (−38.4% [CI, −47.9% to −27.1%]; $P <$ 0.001), and combination therapy/combination therapy group (−75.0% [CI, −78.8% to −70.6%]; $P <$ 0.001). The decrease in the estrogen/placebo group at month 36 was significantly less than that in the alendronate/placebo group (difference, −24.1% [CI, −37.6% to −10.6%]; $P <$ 0.001) or the combination therapy/placebo group (difference, −24.1% [CI, −38.2% to −10.1%]; $P =$ 0.001) but did not differ from that in the placebo group (**Figure** 4). Similar trends were observed for levels of bone-specific alkaline phosphatase.

Safety and Tolerability

Concomitant therapy with alendronate and estrogen for up to 3 years was well tolerated and had a favorable safety profile, consistent with those of the individual treatments (7). During year 3, the overall proportion of all clinical adverse experiences was similar among patients who were switched from treatment groups to placebo. The proportion of gastrointestinal adverse events was also similar in all groups. Although women who continued to receive combination therapy during year 3 experienced a greater number of serious adverse events than did women taking placebo, these events were not related to any specific medical problem or single organ system. The only serious upper gastrointestinal adverse event, erosive esophagitis, occurred in one patient who received placebo during year 3. Similar proportions of patients in the five treatment groups discontinued therapy because of a clinical adverse event. During year 3, no clinically meaningful differences were seen among the groups in laboratory adverse events.

DISCUSSION

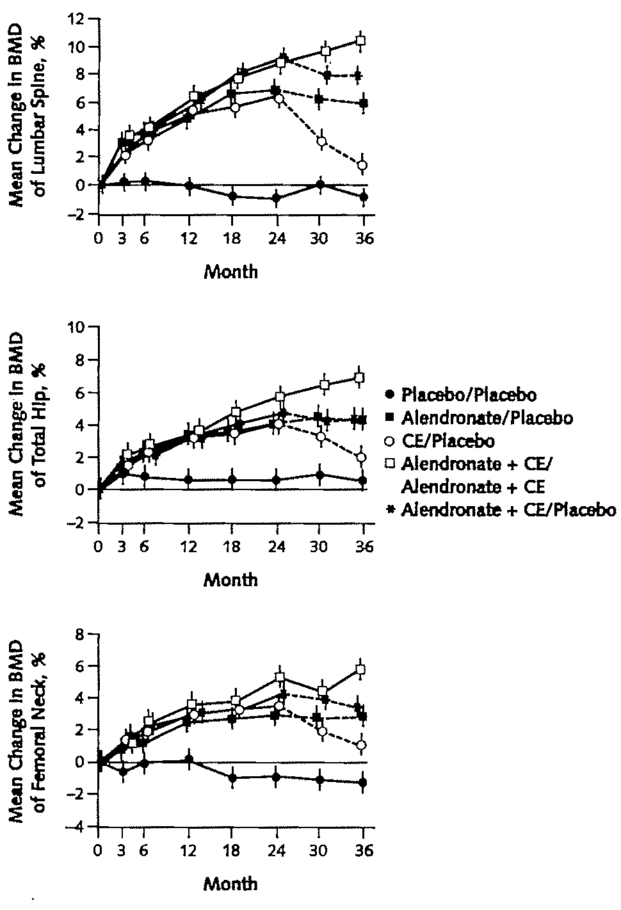
Postmenopausal women with hysterectomy who received estrogen for 2 years and were then switched to placebo for year 3 had a statistically significant loss of bone mineral density at the spine (4.5%), total hip (1.8%), femoral neck (2.4%), and trochanter (2.4%) during the third year. In contrast, women who received alendronate alone or in combination with conjugated estrogens for 2 years and were then switched to placebo for year 3 maintained gains in spine and hip bone mineral density that were attained during the preceding 2 years. At 3 years, bone mineral density at the spine, femoral neck, and trochanter was significantly higher in the group taking alendronate or combination therapy and switched to placebo than in the group previously taking estrogen. Women who continued taking combination therapy with alendronate and conjugated estrogen for a third year had a spine bone mineral density that was 11.3% higher and a hip bone mineral density that was 6.6% higher than those in the placebo group.

The finding of accelerated bone loss after discontinuation of hormone replacement therapy supports results of previous epidemiologic studies and clinical investigations. The Framingham Study, an epidemiologic study begun in 1948, assessed bone mineral density 40 years later in the female half of the cohort that was still alive. Of the 670 women examined, no differences in bone mass were observed between those who had taken hormone replacement therapy for less than 7 years and those who had never taken hormone replacement therapy (14). In a clinical trial by Christiansen and colleagues, 18 postmenopausal women who crossed over from estrogen–progesterone therapy to placebo after 2 years lost 2.3% of spine bone mass the following year (9), compared with a continued increase in vertebral bone density in the 16 women who continued therapy during year 3. Moreover, in the Postmenopausal Estrogen/Progestin Intervention trial, women randomly assigned to the placebo group who had used hormone replacement therapy before enrollment lost more bone mineral density at the spine (−5.3%) and hip (−3.9%) than did women who had not previously used hormone replacement (−3.9% from the spine and −1.5% from the hip) (11). In contrast, postmenopausal osteoporotic women who took alendronate, 10 mg/d, for 2 years maintained bone mass for 1 year after therapy was discontinued (12).

Of note, women who took placebo (with calcium supplementation) for 3 years maintained bone mass at the spine and hip. This observation has been noted in other studies, in which older postmenopausal women taking supplementary calcium maintain or have a slight increase in vertebral bone mineral density (1–3) and maintain or lose bone at different regions of the hip (1–3).

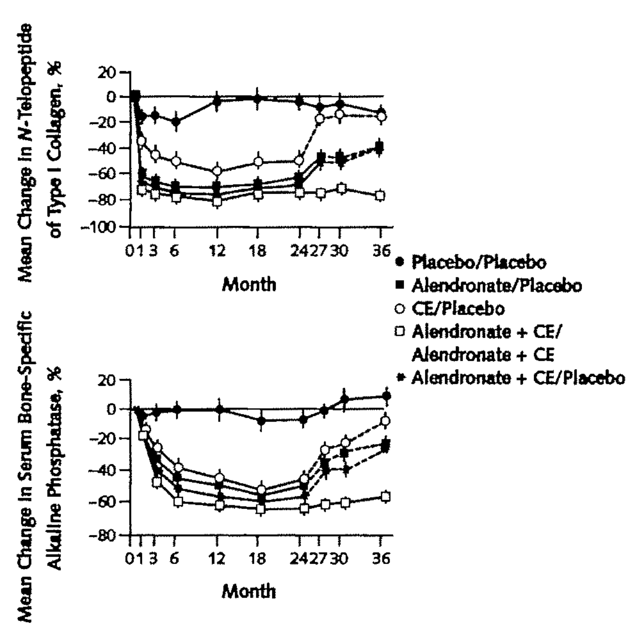
More important, several epidemiologic studies have demonstrated that previous use of hormone replacement therapy does not decrease a woman's risk for fracture (15–17). In a subset of 1720 women from the Framingham observational cohort study, use of estrogen during the 2 years before the study visit resulted in a statistically significant 66% reduction in hip fracture, whereas no significant reduction was noted in patients with past estrogen use (16). In the Study of Osteoporotic Fractures, a lower incidence of nonvertebral fractures was associated only with current use of hormone replacement therapy, not with previous use (17). A study of 1327 Swedish women 50 to 81 years of age showed that current users of hormone replacement therapy had a 65% lower incidence of hip fracture than did women who had never used estrogen. Former users within the past 5 years had a 24% lower incidence of hip fracture, but this value was not statistically significant (15). Our data may explain the finding that current estrogen use is necessary for reduction in fractures. When estrogen therapy is discontinued, bone mass decreases and protection against fracture may be diminished.

Figure 3. **Mean percentage change from baseline to year 3 in bone mineral density (*BMD*).**



Vertical lines represent SEs. Dotted lines represent placebo period. CE = conjugated estrogen.

Figure 4. **Mean percentage change from baseline to year 3 in biochemical markers of bone turnover.**



Data were obtained from per-protocol analyses. Data on urinary *N*-telopeptide cross-links of collagen type I and serum bone-specific alkaline phosphatase, respectively, were available in the following numbers of patients: 26 and 27 in the placebo/placebo group, 38 and 39 in the alendronate/placebo group, 72 and 74 in the conjugated estrogen (*CE*)/placebo group, 35 and 36 in the combination therapy/combination therapy group, and 32 and 33 in the combination therapy/placebo group. Dotted lines represent placebo period.

Our study has several limitations. First, we focused on differences in bone mineral density and safety of therapy. Measurement of fracture as an outcome was not a primary objective. However, recent data suggest that greater improvements in bone mass with alendronate therapy lead to greater reduction in fractures (4, 5). Second, of the 425 postmenopausal women in the original study, 320 (75%) completed 2 years of treatment and 244 (57%) consented to the third year. Nevertheless, the study retained the power to show important differences regarding accelerated bone loss after discontinuation of hormone replacement therapy and continued improvement in bone mass during the third year of combination therapy. In addition, at the beginning of year 3, bone mineral density was similar in women taking estrogen or alendronate who were switched to placebo. The difference in the rate of bone loss in the estrogen group does not appear to be due to a difference in bone mineral density between the estrogen and alendronate groups at the beginning of year 3. Finally, the changes in bone mineral density represent mean changes of a group and may not be significant for a single patient, in whom the least significant change must be taken into account. For example, as a group, women who were taking estrogen and switched to placebo lost 1.8% of bone mineral density at the total hip, a statistically significant decrease. If the calculated precision error at the total hip was 1.2%, a difference of 3.3% would be needed to be 95% confident of a statistically significant change in total-hip bone mineral density for an individual patient at follow-up.

The biochemical markers of bone turnover in our study help explain some of the changes in bone mineral density observed during year 3. Women in the estrogen/placebo group had an increase in urinary levels of *N*-telopeptide cross-links of collagen type I, a marker of bone resorption, that reached the postmenopausal baseline level, while bone mineral density decreased significantly at the spine and hip. However, increases in urinary levels of *N*-telopeptide cross-links of collagen type I were also noted in the other groups that discontinued active therapy, although the absolute level was less than that found in the estrogen/placebo group and bone mineral density in these women did not change significantly. In contrast, women who continued to take combination therapy for the third year maintained the previous level of urinary *N*-telopeptide cross-links of collagen type I in a premenopausal range, and bone mass of the spine and hip continued to improve. Although biochemical markers vary significantly from day to day (18–20), group changes in these markers with therapy are predictive of changes in bone mass (19) and partially reflect the changes in bone mass that we observed. Because a higher level of bone resorption may be an independent risk factor for fracture (21), further studies are needed to determine the clinical effect of an increase in bone resorption after discontinuation of antiresorptive therapy.

Our study lays the foundation for a new and important area of investigation that is relevant to clinical practice. In addition to examining bone mass improvements and fracture reduction with treatment, we must examine these outcomes when antiresorptive therapy is discontinued.

From University of Pittsburgh, Pittsburgh, and Radiant Research Reading, Wyomissing, Pennsylvania; Beth Israel Deaconess Medical Center, Boston, Massachusetts; Michigan Bone and Mineral Clinic, Detroit, Michigan; San Diego Endocrinology and Medical Clinic, San Diego, California; Medical University of South Carolina, Charleston, South Carolina; Virginia Commonwealth University, Richmond, Virginia; Research for Health, Houston, and SAM Clinical Research Center, San Antonio, Texas; Chicago Center for Clinical Research, Chicago, Illinois; Bethesda Health Research, Bethesda, Maryland; Medical College of Georgia, Augusta, Georgia; and Merck and Co., Inc., Rahway, New Jersey.

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She works, always, against the fear of relapse. First come the headaches, which are not in any way ordinary pain ("headache" has always seemed an inadequate term for them, but to call them by any other would be too melodramatic). They infiltrate her. They inhabit rather than merely afflict her, the way viruses inhabit their hosts. Strands of pain announce themselves, throw shivers of brightness into her eyes so insistently she must remind herself that others can't see them. Pain colonizes her, quickly replaces what was Virginia with more and more of itself, and its advance is so forceful, its jagged contours so distinct, that she can't help imagining it as an entity with a life of its own.

Michael Cunningham
The Hours
New York: Farrar, Straus and Giroux; 1998:70

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

Reversal of Warfarin-Induced Excessive Anticoagulation with Recombinant Human Factor VIIa Concentrate

Ruby Anne E. Deveras, MD, and Craig M. Kessler, MD

Background: **Bleeding associated with warfarin anticoagulation correlates directly to duration and degree of international normalized ratio (INR) elevation above the therapeutic range. Safe and rapid reversal of excessive anticoagulation is occasionally needed to treat or avoid hemorrhagic complications.**

Objective: **To evaluate the efficacy and safety of human recombinant factor VIIa (rFVIIa) concentrate in persons requiring rapid reversal of the effects of warfarin.**

Design: **Uncontrolled case series.**

Setting: **Academic medical center.**

Patients: **13 patients with critically increased INRs requiring immediate reversal of warfarin-induced anticoagulation.**

Measurements: **Prothrombin time and INR were measured before and after administration of varying doses of rFVIIa.**

Results: **Critically prolonged INR and bleeding complications were treated successively and rapidly in all patients, regardless of rFVIIa dose (range, 15 to 90 μg/kg of body weight). Indications for use of rFVIIa included an INR greater than 10 in high-risk persons (*n* = 5), clinical hemorrhage (*n* = 4), and diagnostic or therapeutic procedures (*n* = 4).**

Conclusion: **Safe, rapid, and effective administration of rFVIIa corrects critically prolonged INRs and can avert or reverse bleeding associated with warfarin anticoagulation.**

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Warfarin, the most widely prescribed oral anticoagulant therapy in North America (1), is administered to treat or prevent primary and secondary venous and arterial thromboembolic complications. Prolonged use for many years may be necessary, particularly for treating symptomatic hypercoagulability, chronic atrial fibrillation, maintaining mechanical prosthetic heart valves, and preventing acute myocardial infarction and stroke (2). Warfarin therapy has a narrow risk-to-benefit profile. Its complex pharmacokinetics are influenced by concurrent medications, ethanol ingestion, variability of vitamin K intake and absorption, and hepatic disease (3). Therefore, it is not surprising that the most common complication of warfarin use is adverse bleeding (4).

For patients receiving warfarin, estimated yearly risks are 0.6% for fatal bleeding, 3.0% for major hemorrhage, and 9.6% for minor events (5). The incidence of bleeding complications is directly proportional to the intensity of anticoagulation (6) and time spent at a high international normalized ratio (INR) (7). Various strategies have been implemented to reverse warfarin-induced excessive anticoagulation. In a patient with a prolonged INRs without active bleeding but with an anticipated high risk for bleeding, the INR can be decreased slowly by administering an exogenous source of vitamin K_1 (8).

The reversal of active bleeding or excessively elevated INRs in patients with a high risk for bleeding requires rapid replacement of vitamin K–dependent coagulation proteins. This replacement has traditionally been achieved by transfusing fresh-frozen plasma (9) or prothrombin complex concentrates (10). Problems associated with transfusing fresh-frozen plasma are the long time necessary to administer large volumes, a patient's inability to tolerate increases in intravascular volumes, and the potential for transmission of pathogenic blood-borne viruses (11) or prions. Prothrombin complex concentrates work very rapidly but may be thrombogenic (12) and may transmit non–lipid-enveloped pathogens. Therefore, it is important to identify alternative agents that are safe, reliable, and rapidly acting.

We describe the successful use of recombinant factor VIIa (rFVIIa) concentrate in 13 adults receiving warfarin who required rapid reversal of a critically prolonged INR and excessive anticoagulation.

METHODS

Recombinant FVIIa

NovoSeven (Novo Nordisk, Princeton, New Jersey) is a genetically engineered concentrate of human coagulation FVIIa, which is structurally similar to native human plasma–derived FVIIa. The FVII zymogen is synthesized in vitro by a baby hamster kidney-cell line, which is then auto-activated through sequential ion exchange chromatography. This process also enhances eradication of any contaminating murine viruses. No exogenous human serum proteins are used in the manufacturing procedure (13).

The rFVIIa product was developed to achieve hemostasis in persons with hemophilia who have allogeneic antibody inhibitors directed against factor VIII or IX. Essentially, rFVIIa, complexed with tissue factor on phospholipid-rich membranes of activated platelets, mediates conversion of coagulation factor IX to IXa and factor X to Xa. Subsequently, the prothrombinase complex (factors Xa and Va and phospholipid) produces a procoagulant "burst," which is derived from prothrombin conversion to thrombin (14). Thrombin then proteolyzes fibrinogen to fibrin, which is essential for thrombus formation and cross-linking. Clot stability is further promoted by rFVIIa-

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induced activation of thrombin-activated fibrinolytic inhibitor.

Patients

Between 1 September 1999 and 31 October 2001, we considered administration of rFVIIa concentrate in patients referred to the Hematology Service of Georgetown University, Washington, DC, for evaluation and rapid reversal of anticoagulation effects produced by warfarin. Recombinant factor VIIa was prescribed when clinically significant bleeding was precipitated or exacerbated by anticoagulation; when persons assessed to be at high risk for bleeding (INR > 10) could not tolerate infusions of fresh-frozen plasma because of intravascular volume constraints or comorbid conditions; when very rapid warfarin reversal was required; or when interruption of anticoagulation was deemed risky but temporary moderation of warfarin was indicated (for example, for invasive therapeutic or diagnostic procedures).

The dose of rFVIIa to be administered was based on the patient's weight, rounded off to the closest vial size (1.2 mg and 4.8 mg). The first patient received 90 μg/kg of body weight, the recommended dose for persons with hemophilia and alloantibody inhibitors. Subsequent patients were treated with progressively lower doses as it became apparent that even doses in the 15 to 20 μg/kg range (**Table**) provided adequate hemostasis. Recombinant factor VIIa was administered intravenously over 3 to 5 minutes. Prothrombin time and INR were obtained before and after treatment in all persons in order to monitor the effects on coagulation. In addition, factors II, VII, IX, and X activity levels were concurrently measured in four patients. One patient received rFVIIa on two separate occasions.

RESULTS

Thirteen adult patients received decreasing single doses of rFVIIa concentrate as our experience and confidence in the product increased (**Table**). In all patients, the INR was immediately reduced after a single infusion (**Figure**). Prothrombin times and INRs slowly increased with time after administration of rFVIIa but remained below baseline levels for all patients. Subsequent management of patients after rFVIIa administration was individualized according to clinical situation and treatment goals. Most patients resumed warfarin therapy at appropriately adjusted doses within 12 hours after the INR normalized. Patients with an INR greater than 10 also received supplemental vitamin K_1 for long-term protection against relapse.

Four vitamin K–dependent coagulation proteins (factors II, VII, IX, and X) were assayed in four patients 1 hour before and 1 hour after rFVIIa infusion. The activity of these proteins was markedly deficient, which is consistent with the effects of warfarin. Of interest, the activity level of factors II, IX, and X did not appreciably increase after rFVIIa treatment. However, FVII activity increased dramatically (by more than 500%) (data not shown).

Context

Traditional treatments (fresh-frozen plasma, prothrombin complex concentrate) for rapid reversal of excessive anticoagulation from warfarin are limited by inconvenience and potentially serious side effects.

Contribution

This prospective case series showed that a single infusion of human recombinant factor VIIa concentrate (rFVIIa) immediately reduced international normalized ratios without adverse effects in 13 patients who needed rapid reversal of excessive warfarin-induced anticoagulation for various reasons.

Cautions

Before changing treatment policy on the basis of these preliminary findings, physicians should watch for controlled studies that compare outcomes, side effects, and costs in patients treated with rFVIIa versus traditional therapies.

–The Editors

The clinical scenarios in this series varied but were typical of a large hospital experience. Four patients presented with clinically significant hemorrhage, consisting of retroperitoneal bleeding, severe protracted epistaxis, tongue laceration, and an expanding facial and soft palate hematoma. Immediate cessation of bleeding was clinically apparent after rFVIIa administration. Five patients required rapid reversal of anticoagulation effects before invasive, diagnostic, or surgical interventions. These included removal of an arterial femoral sheath, removal of epidural and central venous catheters, closed fixation of a femoral neck fracture, and electrophysiologic studies with pacemaker placement. No adverse bleeding occurred in any persons during or after surgery. In several patients who had recurrent hypercoagulable events or had previous episodes of heparin-induced thrombocytopenia, the risk for bleeding was reduced without complete reversal of anticoagulation effects. Hemorrhagic complications were averted in patients with significant comorbid conditions (**Table**) and a high risk for bleeding, including an INR greater than 10, recent upper gastrointestinal bleeding or history of peptic ulcer disease, quantitative and qualitative platelet dysfunction, hemodialysis, and congestive heart failure.

All patients had indications for chronic or lifelong use of warfarin before treatment with rFVIIa (**Table**). Most patients had received anticoagulation for at least 3 months. In one patient, initiation of warfarin therapy after surgery produced excessive anticoagulation effects within 3 days.

DISCUSSION

This series represents the first substantial experience with rFVIIa concentrate to reverse the effects of excessive

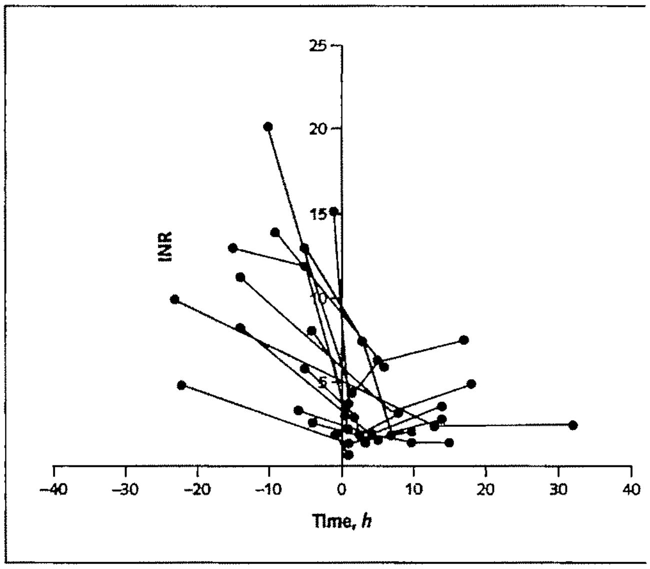
Table. **Characteristics of 13 Patients Treated with Recombinant Factor VIIa***

Patient	Age	Sex	Reason for Anticoagulation	Comorbid Conditions	Treatment Indication	rFVIIa Dose (Total Dose)	INR		PT	
							Before Treatment	After Treatment	Before Treatment	After Treatment
	y					*μg/kg (μg)*			*s*	
1	81	M	Chronic atrial fibrillation, cerebrovascular accident	Chronic renal insufficiency	Retroperitoneal bleeding	90 (6000)	9.95	2.37	51.1	21.4
2	57	F	Chronic atrial fibrillation	Hemodialysis	Closed reduction and internal fixation, left femoral neck fracture	85 (4800)	4.91	1.35	33.3	15.2
3	55	F	Aortic valve replacement	Congestive heart failure	Critically elevated INR, increased risk for hemorrhage, presyncopal symptoms	85 (4800)	>20.00	4.20	>60.0	30.2
4	67	F	Congestive heart failure, chronic atrial fibrillation	Peptic ulcer disease, recent upper gastrointestinal bleeding	Profuse, severe epistaxis	70 (3600)	12.96	7.37	>60.0	42.6
5	62	M	Peripheral vascular disease	Coronary artery disease, unstable angina, hemodialysis	Epidural catheter removal	45 (2400)	8.25	1.94	45.6	19
6	55	F	Heparin-induced thrombocytopenia	Chronic lymphocytic leukemia	Tongue laceration	20 (1200)	13.90	5.86	44.8	37.1
7†	41	M	DVT, antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, hirudin antibodies	Chronic renal insufficiency, peptic ulcer disease, recent upper gastrointestinal bleeding	Arterial sheath removal, critically elevated INR, increased risk for hemorrhage	14 (1200) 14 (1200)	3.37 14.93	1.67 3.65	26.5 59.0	17.4 26.5
8	56	M	Cerebrovascular accident, mitral valve replacement	Coronary artery disease, congestive heart failure, pulmonary edema	Expanding facial hematoma, pulmonary edema, neurologic symptoms	12 (1200)	5.81	2.93	29.8	17.8
9	38	M	DVT, methyltetrahydrofolate reductase and factor V Leiden gene mutations	Coronary artery disease	Critically elevated INR, easy bruising, increased risk for hemorrhage	15 (1200)	6.20	2.09	35.8	19.3
10	74	M	Heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria	Thrombocytopenia, chronic hemolysis, peptic ulcer disease	Electrophysiologic study (ablation), pacemaker placement	12 (1200)	2.57	1.62	21.7	27.0
11	73	F	Chronic atrial fibrillation	Autologous stem-cell transplantation	Removal of Hickman catheter	17 (1200)	1.85	0.73	18.0	10.6
12	44	M	Recurrent DVT	Thrombocytopenia, alcohol abuse	Critically elevated INR, increased risk for hemorrhage	15 (1200)	11.87	3.16	51.8	24.4
13	81	F	Ceberovascular accident	Dilated cardiomyopathy with congestive heart failure	Critically elevated INR, increased risk for hemorrhage	25 (1200)	8.95	3.16	43.1	24.4

* DVT = deep venous thrombosis; F = female; INR = international normalized ratio; M = male; PT = prothrombin time, rFVIIa = recombinant factor VIIa.
† Patient 7 received treatment twice.

warfarin-induced anticoagulation. Thirteen persons who had been taking warfarin received rFVIIa to treat active, symptomatic bleeding; to ameliorate high risks for bleeding; or to reverse anticoagulation preceding invasive diagnostic or therapeutic interventions. The regimen was safe, rapidly acting, and effective in all patients. Substantially lower doses than those recommended for persons with hemophilia and alloantibody inhibitors were used to achieve hemostasis, perhaps reflecting the otherwise normal coagulation mechanism in patients with warfarin-induced anticoagulation.

Figure. **The international normalized ratios (*INRs*) of 13 patients relative to treatment with recombinant factor VIIa.**



The 0 on the x-axis represents the time at which the dose was administered. Each line represents a patient with his or her INR. The trends in INR and prothrombin time improvement were identical for all patients.

Preclinical studies in rats (15) and normal humans who ingested acenocoumarol (16) have demonstrated the safety and feasibility of rFVIIa use in the clinical setting. Recent anecdotal reports have supported the potential effectiveness of rFVIIa for reversing warfarin-induced excessive anticoagulation to facilitate surgery (17) or treat serious bleeding complications (18, 19). Our series extends the clinical experience with rFVIIa outside the hemophilia population and shows the ease and flexibility of rFVIIa administration in patients who require moderation of anticoagulation effects but are concurrently at increased risk for hypercoagulable events if their anticoagulation was completely reversed. Examples include our patient with active heparin-induced thrombocytopenia and hirudin antibodies and our patients with mechanical heart valves, in whom only brief interruptions of anticoagulation are desirable.

A limitation of using rFVIIa is the inability to monitor or predict hemostatic efficacy in the laboratory. Prothrombin times and FVII activity levels do not correlate. Therefore, we relied on clinical assessment, that is, cessation of bleeding, stability of hematocrit, and other clinical measures. The lack of rFVIIa effects on other vitamin K–dependent clotting factors corroborates the hypothesis that the "thrombin burst" generated on activated platelet surfaces is critical to the hemostatic success of rFVIIa.

Recombinant factor VIIa concentrate will not transmit blood-borne pathogens. Its high specific activity obviates the volume constraints of replacement therapy with fresh-frozen plasma and substantially reduces the time necessary for administration and for achieving adequate hemostasis. Despite the rare reports of hypercoagulable complications associated with rFVIIa (20), no thromboembolic events were observed in our small series, which included elderly persons with underlying atherosclerosis.

Adequate hemostasis was achieved with very low doses (range, 15 to 20 μg) of rFVIIa. As a result, our regimen is more cost competitive with fresh-frozen plasma. Because rFVIIa concentrate is expensive (approximately \$1.40/μg Average Wholesale Price in 2002), our Blood Bank monitors requests for rFVIIa with individual patient assessment by hematologists for off-label indications. Institutional guidelines for rFVIIa reversal of excessive warfarin-induced anticoagulation would be prudent.

In summary, rFVIIa concentrate was used successfully and safely to reverse warfarin toxicity in a diverse population of patients. Prospective studies are necessary to determine the most optimal and cost-effective dosing regimen.

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Potential Financial Conflicts of Interest: *Consultancies:* R.A.E. Deveras, C.M. Kessler. *Honoraria:* C.M. Kessler.

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"Are you being properly looked after?" Bergotte asked me. "Who is treating you?" I told him that I had seen, and should probably go on seeing, Cottard. "But that's not at all the sort of man you want!" he told me. "I know nothing about him as a doctor. But I've met him at Mme Swann's. The man's an imbecile. Even supposing that that doesn't prevent his being a good doctor, which I hesitate to believe, it does prevent his being a good doctor for artists, for intelligent people. People like you must have suitable doctors, I would almost go so far as to say treatment and medicines specially adapted to themselves. Cottard will bore you, and that alone will prevent his treatment from having any effect . . . How do you expect Cottard to be able to treat you? He has made allowances for the difficulty of digesting sauces, for gastric trouble, but he has made no allowance for the effect of reading Shakespeare."

Marvel Proust
Remembrance of Things Past (Within a Budding Grove)
New York: Vintage Books; 1981:614

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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

COMPLEMENTARY AND ALTERNATIVE MEDICINE SERIES
Series Editors: David M. Eisenberg, MD, and Ted J. Kaptchuk, OMD

Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer

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Many patients with cancer use complementary and alternative medical (CAM) therapies. Physicians need authoritative information on CAM therapies to responsibly advise patients who seek these interventions. This article summarizes current evidence on the efficacy and safety of selected CAM therapies that are commonly used by patients with cancer. The following major categories of interventions are covered: dietary modification and supplementation, herbal products and other biological agents, acupuncture, massage, exercise, and psychological and mind–body therapies. Two categories of evidence on efficacy are considered: possible effects on disease progression and survival and possible palliative effects. In evaluating evidence on safety, two types of risk are considered: the risk for direct adverse effects and the risk for interactions with conventional treatments. For each therapy, the current balance of evidence on efficacy and safety points to whether the therapy may be reasonably recommended, accepted (for example, dietary fat reduction in well-nourished patients with breast or prostate cancer), or discouraged (for example, high-dose vitamin A supplementation). This strategy allows the development of an approach for providing responsible, evidence-based, patient-centered advice to persons with cancer who seek CAM therapies.

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For author affiliations, see end of text.

In this article, we summarize the current scientific medical literature on complementary and alternative medical (CAM) therapies commonly used by persons with cancer. We focus on evidence about disease progression and palliation rather than cancer prevention. For this paper, we define CAM therapies as interventions not generally available in hospital-based oncology practices in the United States, with the understanding that some of these therapies are gaining acceptance in the conventional realm and may eventually fail to meet our current definition (1). We examine dietary modification (fat reduction and radical dietary regimens); supplementation with antioxidant vitamins, soy, herbs, and other "natural products"; acupuncture; massage; exercise; and psychological and mind–body interventions. Although patients with cancer often use spiritual approaches, these approaches are beyond the scope of this paper. For supplements, we present major categories of adverse effects and interactions with conventional treatments. Finally, we propose a strategy to engage patients who seek advice about CAM therapies.

METHODS

We collected references from the following sources: databases (searched without restriction to particular years), including MEDLINE, CANCERLIT, AMED, EMBASE, and PsycINFO; Web sites, including the Longwood Herbal Task Force (www.mcp.edu/herbal/), the Center for Alternative Medicine Research in Cancer at the University of Texas–Houston Health Science Center (www.sph.uth.tmc.edu:8052/utcam/therapy.htm; updated information currently available at www.mdanderson.org/cimer), and the National Cancer Institute (www.cancer.gov/cancerinfo/treatment/cam); Medscape's Hematology-Oncology Med-Pulse (electronic newsletter; subscription available at www.medscape.com); Media Watch (electronic mailing list on cancer news; subscription available through lpchef@earthlink.net); bibliographies prepared by experts; recommendations of colleagues; and citations of papers identified from the preceding sources.

In evaluating efficacy of a therapy, we gave results of randomized, controlled trials (RCTs) the highest priority. We evaluated results of uncontrolled trials or observational data only if no RCTs had been completed, and we did not consider evidence from these sources to be conclusive. In evaluating safety of a therapy, we considered both preclinical and clinical data, although we most heavily weighted clinical reports of life-threatening or permanently disabling adverse events.

One of the authors is an employee of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health; therefore, NCCAM approval of the article was required at the time of submission for publication. With this exception, the funding agencies had no role in the collection, analysis, and interpretation of the data or the decision to submit this article for publication.

CRITERIA FOR ADVICE ON CAM THERAPIES

In Table 1, we propose criteria for placing individual therapies along a continuum that ranges from "recommend" to "accept" to "discourage" (2). These criteria allow physicians to use existing data to provide evidence-based advice to patients. We apply these criteria to the therapies evaluated in this paper.

EVIDENCE ON EFFICACY AND SAFETY OF CAM THERAPIES

Tables 2 and 3 briefly summarize the therapies reviewed.

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Table 1. **Criteria Used To Determine Whether a Complementary and Alternative Medical Therapy May Reasonably Be Recommended, Accepted, or Discouraged by Physicians[*]**

Requirements	Recommend	Accept; May Consider Recommending	Accept	Discourage
Basic	Evidence supports both efficacy and safety	Evidence supports both efficacy and safety	Evidence on efficacy is inconclusive but evidence supports safety	Evidence indicates either inefficacy or serious risk
Efficacy	≥3 RCTs have evaluated the therapy ≥75% of trials support efficacy or a meta-analysis of trials supports efficacy For ≥3 of the trials that support efficacy: Trial has >50 patients *and* Trial is of adequate quality[†] Evidence supporting efficacy must come from >1 research team	≥1 RCT has evaluated the therapy >50% of trials support efficacy Evidence supporting efficacy fails to meet the criteria for therapies that may be recommended	Existing evidence is inadequate to conclude whether the therapy is effective or ineffective Data on efficacy fail to meet the criteria for considering recommendation Data on efficacy fail to meet the criteria for discouragement	≥2 RCTs have evaluated the therapy ≥67% of trials suggest that the therapy is ineffective For ≥2 of the trials that suggest lack of efficacy: Trial has >50 patients *and* Trial is of adequate quality[†]
Safety[‡]	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	There is reliable documentation of a major (life-threatening or permanently disabling) adverse event occurring in association with the therapy *or* Based on current information, a theoretical potential for major adverse events exists

[*] RCT = randomized, controlled trial.

[†] Study quality was assessed for two types of therapies: those supported by RCTs of adequate number and size to qualify for recommendation and those with inefficacy suggested by RCTs of adequate number and size to qualify for discouragement. Quality was assessed by using the Jadad scale, a validated instrument that assigns scores for randomization, blinding, and reporting of withdrawals (3). Studies were rated by 2 authors; discrepancies were resolved by discussion. If double-blinding of a given therapy was both practical and ethical, an aggregate score of 3 points (of a maximum of 5) was considered adequate. If double-blinding was impractical or unethical, a score of 2 points (of a maximum of 3 for unblinded studies) was considered adequate.

[‡] In some instances, a given therapy appears to pose a greater risk for a particular group of patients (e.g., patients undergoing radiation or chemotherapy or patients at increased risk for bleeding); the therapy should therefore be avoided by that group. In such cases, the conclusion that it is generally reasonable to recommend or accept a therapy will be qualified by a list of specific contraindications.

Dietary Modification and Supplementation

Dietary Fat Reduction

Dietary fat reduction has received attention in the treatment of both breast and prostate cancer. With regard to breast cancer, reduction of fat intake has been shown to reduce estrogen levels in both premenopausal and postmenopausal women (4). Survival of postmenopausal patients with resected breast cancer is greater in Japan, where diets are low in fat, than in the United States (5). However, differences between American and Japanese diets go beyond fat content; in particular, soy consumption is higher in Japan. The Nurses' Health Study (a cohort study) did not find evidence of a strong adverse effect of high postdiagnostic fat intake on survival (6). The Women's Intervention Nutrition Study (WINS), an ongoing RCT testing the hypothesis that postdiagnostic reduction of fat intake (to 15% of total calories) will increase survival, should provide more definitive information (**Appendix Table 1**, available at www.annals.org) (5). Currently, evidence is inadequate to recommend dietary fat reduction in women with breast cancer. However, it is reasonable to accept fat reduction in well-nourished patients who elect to try this approach.

Epidemiologic studies suggest that factors in the American diet may promote the progression of latent prostate cancer to the clinical stage. Autopsy studies show that latent prostate cancer occurs at equal rates in men of Asian countries and the United States, whereas clinical prostate cancer is much more common in the United States. Within a generation, Japanese and Chinese men who immigrate to the United States develop a risk for clinical cancer that approaches the U.S. average (7). The hypothesis that fat is at least one contributing dietary factor is supported by several observational studies that suggest a positive association between intake of saturated or animal fat and the progression of prostate cancer (8–11). In summary, observational data suggest that reduction of saturated or animal fat might slow progression of prostate cancer, but data from randomized dietary intervention trials are needed to support specific dietary advice. As with breast cancer, it is currently reasonable for physicians to accept dietary fat reduction in well-nourished men with prostate cancer.

Radical Dietary Regimens

Space does not permit evaluation of all radical dietary regimens used by patients with cancer. Our discussion of macrobiotics, a regimen that has yielded well-publicized testimonials of cancer remission (12, 13), is intended to demonstrate an evaluative approach that can be applied in consideration of other regimens.

Macrobiotic diets are mainly vegetarian, consisting primarily of whole grains (14, 15). Macrobiotic diets are low in fat, and some are high in phytoestrogens (including isoflavonoids, which are derived primarily from soy) (16). Scientific evidence on the potential benefits of macrobiotic diets for patients with cancer is limited to two retrospective studies with serious methodologic flaws (17). No RCTs of macrobiotics have been conducted.

Potential risks are associated with macrobiotics. The macrobiotic philosophy may lead patients to delay or dis-

Table 2. **Complementary and Alternative Medical Therapies Intended To Affect Disease Progression and Patient Survival***

CAM Therapy	Efficacy—Level of Evidence†	Efficacy—Direction of Evidence‡	Level of Risk§ (In the Absence of Specific Contra-indications)	Contra-indications‖	Reasonable Advice¶ (In the Absence of Specific Contra-indications)	References
Reduction of fat intake for breast cancer	II–2	→	1	N	Accept and monitor	6
Reduction of fat intake for prostate cancer	II–2	→	1	N	Accept and monitor	8–11
Macrobiotic diet	III	→	2	E, N	Accept and monitor	16, 17, 19
Vitamin A	I (2 RCTs, n = 307 and n = 29 133)**	→	6	A, T	Discourage and monitor	25, 27, 29–32
Vitamin C	I (2 RCTs, n = 100 and n = 150)	↓	2	A, B	Discourage and monitor	33–38
Vitamin E for latent prostate cancer	I (1 RCT, n = 29 133)	↑ (logical extension of study results)††	1	A, B	Accept (may consider recommending) and monitor	27, 37, 40
Vitamin E for cancer other than latent prostate cancer	III	→	1	A, B	Accept and monitor	37, 40, 173
Soy for breast cancer	III	→	4	A, B, E	Discourage and monitor	41–44, 61, 67–71
Soy for prostate cancer	III	→	1	A, B	Accept and monitor	7, 41, 42, 71
PC-SPES	I (1 RCT, n = 90; only preliminary report available)	→	6	C	PC-SPES currently unavailable	73, 76–81, 91–93
Shark cartilage	III	→	3	H, An	Accept and monitor	94–97, 99–102
Mind–body therapies	I (10 RCTs, n = 63–271; 1 quasi-randomized trial, n = 94)	→	2		Accept and monitor	133, 137, 142, 150–159

* PC-SPES = prostate cancer and "hope" (in Latin); RCT = randomized, controlled trial.

† Level of evidence: Taken from criteria of U.S. Preventive Services Task Force (195). I = evidence obtained from at least one properly designed RCT; II–1 = evidence obtained from well-designed controlled trials without randomization; II–2 = evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group; II–3 = evidence obtained from multiple time series with or without the intervention; III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

‡ Direction of evidence: ↑ = current evidence suggests therapy is effective; ↓ = current evidence suggests therapy is not effective; → = current evidence is inconclusive. ↗ = current evidence is mixed, but most studies suggest therapy is effective; ↘ = current evidence is mixed, but most studies suggest therapy is not effective.

§ Level of risk: Level 4 or higher indicates that it is prudent to discourage a therapy. 6 = documentation of major (life-threatening or permanently disabling) adverse event that occurred in association with therapy in multiple instances with causal relationship established; 5 = documentation of major adverse event that occurred in association with therapy; 4 = theoretical possibility of major adverse event occurring as a result of therapy (based on current understanding of mechanism of action or preclinical data) but no clinical cases documented to date; 3 = documentation of minor adverse event that occurred in association with therapy; 2 = theoretical possibility of minor adverse event occurring as a result of therapy but no clinical cases documented to date; and 1 = no adverse events documented and, theoretically, adverse events seem unlikely.

‖ Contraindications: A = antioxidant. Avoid concurrent use with radiation or chemotherapy (see text for current evidence supporting this contraindication). An = potential inhibitor of angiogenesis. Avoid in pregnancy, childhood, the perioperative period and in patients with vascular insufficiency (including coronary artery disease). B = potential risk for bleeding. Avoid in patients who are receiving anticoagulant therapy or who are thrombocytopenic (for oral agents, also avoid during perioperative period). C = no data on use in combination with radiation or cytotoxic chemotherapy. Until more evidence is gathered, it is prudent to avoid concurrent use. E = phytoestrogen. Avoid in women with breast cancer, especially those with estrogen receptor–positive tumors. In particular, patients taking tamoxifen should be warned of potential interaction. Also avoid in women with endometrial cancer. (See discussion in text of soy supplementation, which presents the current evidence supporting this contraindication.) H = high calcium content. Avoid in patients with history of hypercalcemia. N = restrictive diet. Avoid in patients with poor nutritional status. T = teratogen. Avoid in patients who may be pregnant.

¶ Criteria for final advice: See Table 1.

** See text for full discussion of these RCTs and data from other trials that raise questions about the findings of these two studies.

†† In this study (27), persons taking vitamin E had a significantly decreased incidence of clinical prostate cancer, but the effect on the incidence of latent prostate cancer was not significant. These findings suggest that vitamin E supplementation may prevent progression of latent prostate cancer to clinical prostate cancer.

Table 3. **Complementary and Alternative Medical Therapies Intended for Palliation of Symptoms Associated with Cancer or Side Effects of Conventional Treatment***

CAM Therapy and Problem	Efficacy—Level of Evidence†	Efficacy—Direction of Evidence‡	Level of Risk§ (in the Absence of Specific Contraindications)	Contraindications‖	Reasonable Advice¶ (in the Absence of Specific Contraindications)	References
Acupuncture for chemotherapy-related nausea and vomiting	I (6 RCTs, *n* = 10–104)	↑	3	B	Accept (may consider recommending) and monitor	103–109, 119–121
Acupuncture for chronic pain (related to underlying disease or conventional treatment)	III	→	3**	B	Accept and monitor	103, 111–121
Massage for anxiety	I (2 RCTs, *n* = 7 and *n* = 34)	↑	3	B†† (see text for other cautions)	Accept (may consider recommending) and monitor	122, 123, 129, 130, 196, 197
Massage for pain (related to underlying disease or conventional treatment)	I (3 RCTs, *n* = 34–103)	→	3	B†† (see text for other cautions)	Accept and monitor	122, 124, 125, 129, 130, 196, 197
Massage for nausea (related to autologous bone marrow transplantation)	I (1 RCT, *n* = 34)	↑	3	B†† (see text for other cautions)	Accept (may consider recommending) and monitor	122, 129, 130, 196, 197
Massage (manual lymph drainage) for lymphedema	I (1 RCT, *n* = 28; 1 quasi-randomized trial, *n* = 40)	↑	2	See text for cautions	Accept (may consider recommending) and monitor	126, 127
Exercise to improve physical function and psychological and physical symptoms in patients receiving conventional therapy	I (3 RCTs, *n* = 62–123; 2 quasi-randomized trials, *n* = 50 and *n* = 62)	↑ ‡‡	2	See Appendix Table 6§§ for cautions	Accept (may consider recommending) and monitor	198–202

* RCT = randomized, controlled trial.

† Level of evidence: Taken from criteria of U.S. Preventive Services Task Force (195). I = evidence obtained from at least one properly designed randomized, controlled trial; II–1 = evidence obtained from well-designed controlled trials without randomization; II–2 = evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group; II–3 = evidence obtained from multiple time series with or without the intervention; and III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

‡ Direction of evidence: ↑ = current evidence suggests therapy is effective; ↓ = current evidence suggests therapy is not effective; → = current evidence is inconclusive; ↗ = current evidence is mixed, but most studies suggest therapy is effective; ↘ = current evidence is mixed, but most studies suggest therapy is not effective.

§ Level of risk: Level 4 or higher indicates that it is prudent to discourage a therapy. 6 = documentation of major (life-threatening or permanently disabling) adverse event that occurred in association with therapy in multiple instances with causal relationship established; 5 = documentation of major adverse event that occurred in association with therapy; 4 = theoretical possibility of major adverse event occurring as a result of therapy (based on current understanding of mechanism of action or preclinical data) but no clinical cases documented to date; 3 = documentation of minor adverse event that occurred in association with therapy; 2 = theoretical possibility of minor adverse event occurring as a result of therapy but no clinical cases documented to date; and 1 = no adverse events documented and theoretically, adverse events seem unlikely.

‖ Contraindications: A = antioxidant. Avoid concurrent use with radiation or chemotherapy (see text for current evidence supporting this contraindication). An = potential inhibitor of angiogenesis. Avoid in pregnancy, childhood, the perioperative period and in patients with vascular insufficiency (including coronary artery disease). B = potential risk for bleeding. Avoid in patients who are receiving anticoagulant therapy or who are thrombocytopenic (for oral agents, also avoid during perioperative period). C = no data on use in combination with radiation or cytotoxic chemotherapy. Until more evidence is gathered, it is prudent to avoid concurrent use. E = phytoestrogen. Avoid in women with breast cancer, especially those with estrogen receptor–positive tumors. In particular, patients taking tamoxifen should be warned of potential interaction. Also avoid in women with endometrial cancer. (See discussion in text of soy supplementation, which presents the current evidence supporting this contraindication.) H = high calcium content. Avoid in patients with history of hypercalcemia. N = restrictive diet. Avoid in patients with poor nutritional status. T = teratogen. Avoid in patients who may be pregnant.

¶Criteria for final advice: See Table 1.

** Although there have been case reports of more serious adverse events (such as pneumothorax), such incidents are very unlikely when accepted techniques are used by a competent practitioner.

†† This contraindication applies to deep tissue or forceful massage; gentle massage (including manual lymph drainage, a specialized form of massage used for lymphedema) may be used with caution in patients at increased risk for bleeding.

‡‡ All trials reported benefits for at least one of the following outcomes: physical function, psychological distress, and physical symptoms.

§§ Available at www.annals.org.

continue conventional therapy (14, 18). Limited data suggest that macrobiotic diets may alter the metabolism of some drugs (19). Although it seems that a carefully formulated macrobiotic diet can provide adequate nutrition (20, 21), it seems prudent to avoid highly restrictive diets in poorly nourished patients (22). Because some macrobiotic diets have a high phytoestrogen content, it seems prudent to discourage their use by women with breast cancer (especially those who have estrogen receptor–positive tumors or who are taking tamoxifen) or endometrial cancer (see discussion of soy).

For well-nourished patients who do not have breast or endometrial cancer, it seems reasonable to accept macrobiotics as an adjunct to conventional treatment. Physicians should closely monitor patients who are following macrobiotic diets for signs of malnutrition or altered metabolism of conventional medications.

Antioxidant Vitamin Supplementation

The antioxidant vitamins include vitamin A (comprising both retinol and its carotenoid precursors), vitamin C, and vitamin E (23, 24). Because oxidative damage to cells might increase the risk for cancer, it is plausible that antioxidants could help in the primary prevention of cancer;

however, their potential role in the progression of cancer is less clear. Aside from their antioxidant activity, these vitamins might possibly affect cancer progression through such mechanisms as inducing cellular differentiation or enhancing immune function (23, 25, 26).

The combination of antioxidants with radiation therapy or chemotherapy causes special concern. We discuss this topic later in the paper.

Vitamin A: Specific retinoids (retinol analogues) are used as differentiation agents in the conventional medical treatment of certain cancers; the most notable example is all-*trans* retinoic acid, which is commonly used to induce remission in acute promyelocytic leukemia. However, little evidence exists on the possible effects of nonprescription vitamin A supplements on cancer progression. One RCT suggested that vitamin A might actually promote progression of latent prostate cancer to the clinical stage (with vitamin A, the incidence of clinical tumors increased, whereas the incidence of latent tumors did not) (27). Two other RCTs failed to find any effect of vitamin A on the overall incidence of prostate cancer; however, these studies did not distinguish between latent and clinical cancer (28, 29). In an RCT of vitamin A as adjuvant therapy in patients with stage I non–small-cell lung cancer after curative resection, vitamin A failed to show benefits in terms of tumor recurrence or overall survival, although it seemed to prevent the development of second primary tumors related to tobacco consumption (30). Two much larger RCTs have suggested that vitamin A may actually increase the incidence of lung cancer in high-risk populations (29, 31, 32).

The toxic syndrome known as *hypervitaminosis A* results from intake of very large doses of vitamin A in the form of retinol (this syndrome is not seen with intake of large doses of carotenoids) (25). Two of the trials described earlier (30, 32) administered retinol. Although no signs of hypervitaminosis A were reported in the trial that administered approximately eight times the recommended daily allowance (RDA) (32), typical manifestations of hypervitaminosis A (including hepatotoxicity) were noted in the trial that administered approximately 100 times the RDA (24, 30).

The limited available data suggest little benefit of high-dose vitamin A supplementation and some potential harm. Therefore, at present, it seems prudent to discourage vitamin A supplementation in excess of the RDA.

Vitamin C: Data on vitamin C and cancer progression are limited. Two RCTs ($n = 100$ and $n = 150$), both of adequate quality, failed to show any benefit of high-dose vitamin C in patients with advanced cancer (**Table 1**) (**Appendix Table 2**, available at www.annals.org) (33, 34). Concerning safety, several studies have found that vitamin C has anticoagulant effects (35–38). On the basis of the apparent lack of efficacy of vitamin C, it seems reasonable for physicians to discourage patient use of high-dose vitamin C to treat cancer. For patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery, the risk for bleeding is an additional reason to avoid high-dose vitamin C.

Vitamin E: One RCT suggests that vitamin E supplementation (at a dose of approximately three times the RDA) may prevent progression of latent prostate cancer to clinical cancer (27, 39); however, data are lacking on vitamin E and the progression of clinical cancer. With regard to safety, vitamin E has been shown to diminish platelet function (37, 40). Although it seems generally reasonable for physicians to accept patients' use of vitamin E to treat prostate cancer, patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery should avoid high-dose vitamin E.

Soy Supplementation

Soy may contribute to the suggested protective effects of the Japanese diet on breast cancer survival and progression of latent prostate cancer to the clinical stage (5, 7, 41, 42). Soy products are the major dietary source of isoflavonoid phytoestrogens (41, 42). Isoflavonoids could affect cancer progression through several possible mechanisms.

The weak estrogenic effects of isoflavonoids are of particular interest in relation to breast and prostate cancer. Several studies have focused on mechanisms by which isoflavonoids might limit activity of endogenous sex hormones. Isoflavonoids compete with estradiol for binding sites (as does the antiestrogen tamoxifen) (43). However, in vitro data suggest that, at physiologically relevant concentrations, it is possible for isoflavonoids to enhance rather than inhibit the proliferative effects of estradiol on estrogen-dependent breast cancer cells (44). Isoflavonoids inhibit enzymes involved in estrogen and androgen synthesis (45, 46), and, by stimulating production of sex hormone–binding globulin, could reduce activity of both estradiol and testosterone (47). However, it is not clear that clinically significant effects on sex hormone synthesis or levels of sex hormone–binding globulin would occur at physiologically relevant concentrations (43, 45–48). Several RCTs have studied the hormonal effects of increasing isoflavonoid intake in women; most have not demonstrated significant decreases in estrogen levels or increases in sex hormone–binding globulin (49–56). In men, isoflavonoids might reduce testosterone levels by acting on the hypothalamus and pituitary gland (as does the synthetic estrogen diethylstilbestrol [DES]), although RCTs to date do not support such an effect (57, 58).

Potential antitumor effects of the isoflavonoid genistein go beyond interactions with sex hormones—inhibition of tyrosine kinases (59) and topoisomerase II (60), suppression of in vitro cell proliferation (41, 43, 47, 60–63), and inhibition of angiogenesis in vitro (64, 65). However, these effects require concentrations that may exceed levels attainable in vivo with oral administration (43, 48). Studies of oral genistein supplementation in animal models of hormone-independent cancer have produced mixed results (63, 66).

In breast cancer, the net effects of isoflavonoids will be determined by the balance of three factors: pro-estrogenic effects, potential inhibition of the effects of endogenous estrogens, and possible antitumor effects unrelated to estrogenic activity. No clinical data are currently available on the effects of soy supplementation on breast cancer progression, but evidence suggests that harmful pro-estrogenic effects may occur in some patients (43, 44, 61, 67–70). Dietary soy can stimulate the growth of estrogen-dependent tumors in mice, and two small studies suggest that soy supplementation may cause estrogenic stimulation of the breasts in premenopausal women (67–69).

At present, it seems prudent to discourage soy supplementation in women with breast cancer (especially those with estrogen receptor–positive tumors) or endometrial cancer. Because data obtained from an animal study indicate that genistein can negate the inhibitory effect of tamoxifen on breast cancer growth, women taking tamoxifen should especially avoid soy supplements (70).

No published clinical studies evaluate the effects of soy supplements on prostate cancer progression. However, unlike with breast cancer, the pro-estrogenic activity of isoflavonoids might possibly have benefits in prostate cancer. A federally funded RCT is currently testing isoflavonoids as an adjunct to androgen ablation therapy (**Appendix Table 3**, available at www.annals.org). Currently, it seems reasonable to accept the use of soy supplements by patients with prostate cancer who elect to try them.

Because isoflavonoids have antioxidant activity, the combination of soy supplements with radiation therapy or chemotherapy causes special concern (42). Isoflavonoids may inhibit platelet aggregation in nonhuman primates (71); thus, it seems prudent for patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery to avoid soy supplements.

Herbal Products and Other Biological Agents: Selected Examples

Given the numerous herbal products and other biological agents used by patients with cancer, discussion of all such supplements is beyond the scope of this paper. Instead, we focus on PC-SPES and shark cartilage as examples of supplements that are purported to slow disease progression. Our discussion of these examples demonstrates an evaluative approach that can be applied to other supplements.

PC-SPES

PC-SPES ("PC" refers to prostate cancer; "spes" means "hope" in Latin) (BotanicLab, Brea, California) is purported to slow the progression of prostate cancer and to increase quality of life. It is an oral supplement composed of extracts of eight herbs (**Appendix Table 4**, available at www.annals.org). Estrogenic properties have been reported for licorice and *Panax* species (72), which are among the herbal components of PC-SPES, and specific phytoestrogens have been identified in the product (73–75). The synthetic estrogen DES has also been detected in some samples of PC-SPES (see discussion of contamination). Several studies of PC-SPES have demonstrated estrogenic effects in vitro (73, 76), in mice (76), and in humans (76–81). Nevertheless, in vitro activity of PC-SPES cannot be explained solely by estrogenic effects. In vitro sensitivity of tumor cell lines to PC-SPES cannot be predicted by the presence or absence of sex hormone receptors (82), and PC-SPES shows transcriptional effects in androgen-sensitive prostate cancer cells that are distinct from those of DES or estradiol (83).

In vitro studies document that PC-SPES inhibits growth of various cancer cell lines, including both androgen-sensitive and androgen-insensitive prostate cancer cells (73, 82–88). Preclinical data support potential antitumor activity of specific phytochemicals found in PC-SPES (73, 74, 89, 90). However, studies in mice that examined the effects of PC-SPES on the growth of androgen-insensitive human prostate carcinoma cells have produced mixed results (80, 87).

Five open-label studies suggest that PC-SPES can decrease levels of prostate-specific antigen (PSA) (76–78, 80, 81), stabilize or improve metastatic disease (81), reduce pain (78), and increase quality of life (78). These studies reported PSA decreases of more than 50% in most patients (76–78, 80, 81), even in men refractory to conventional hormone-ablative therapy (77, 78, 80, 81). Preliminary results from a small RCT ($n = 90$) of PC-SPES in hormone-refractory patients showed PC-SPES to be more effective than DES in reducing PSA (although significance was borderline) (91). The effect of PC–SPES on survival has not yet been investigated.

Many of the reported adverse effects of PC-SPES may result from its estrogenic properties—thrombotic events (noted in approximately 3% of patients) (76–78, 80, 81, 91, 92), breast tenderness or enlargement (76–81), sexual dysfunction (76, 79, 81), hot flashes (77, 80, 81), edema (77, 79), decreased body hair (79), and hypertriglyceridemia (81). In contrast with many reports of thrombotic events (76, 78, 80, 81, 91, 92), a case report of profound bleeding diathesis suggests an anticoagulant effect of PC-SPES (93). In another case report, PC-SPES use was associated with increased international normalized ratio in a patient taking warfarin (92). Other reported adverse effects include gastrointestinal symptoms (77, 78, 81), leg cramps (77, 81), fatigue (77, 81), and allergic reactions (81). No data on potential interactions between PC-SPES and radiation therapy or cytotoxic chemotherapy are available.

Recent analyses have revealed contamination of PC-SPES with conventional medications (DES, warfarin, and indomethacin) (73, 91, 93). Two studies found variable amounts of DES in most PC-SPES samples tested (73, 91), although two other studies failed to find evidence of DES contamination in analyzed samples (76, 83). Because DES has shown clinical efficacy against prostate cancer, the discovery of DES contamination raises the question of whether observed clinical results can be attributed to PC-SPES herbal components (73). One study found that antineoplastic potency in vitro correlated with DES content of PC-SPES samples (73). However, in the RCT described earlier (91), the effects of PC-SPES seemed to go beyond those attributable to DES. Although patients in the PC-SPES group of the study received only 0.01% to 3.1% of the DES dose administered to patients in the DES group, PC-SPES seemed to be more effective than DES (91). Investigation of the above-mentioned case of profound bleeding diathesis suggested warfarin contamination of PC-SPES; the presence of warfarin was subsequently verified in some PC-SPES samples (naturally occurring phytocoumarins are likely to be present in PC-SPES as well) (73, 93). A third drug, indomethacin, has also been detected in PC-SPES (73). In addition to variable contamination with conventional medications, considerable intersample variation has been found in the levels of potentially active phytochemicals (73). In February 2002, the Food and Drug Administration (FDA) warned patients to stop taking PC-SPES. The sole manufacturer issued a recall and subsequently went out of business. PC-SPES is currently unavailable.

Preliminary evidence supporting efficacy of PC-SPES is provocative. However, its use has been associated with major adverse events, and analysis indicates both contamination with conventional medications and variation in levels of potentially active natural compounds. Advice on the use of PC-SPES must await reintroduction of a product that is proven to be free of conventional medications and well-standardized for phytochemical components, particularly phytoestrogens and phytocoumarins. The case of PC-SPES highlights the lack of adequate quality control in the herbal industry today.

Shark Cartilage

Current evidence indicates that cartilage contains proteins that inhibit angiogenesis. Although angiogenesis inhibitors could prove useful in cancer treatment, commercial shark cartilage products are intended for oral or rectal administration, making it unlikely that antiangiogenic proteins would enter the circulation intact. **Appendix** Table 5 (available at www.annals.org) summarizes data on potential mechanisms of action of cartilage products.

Current clinical evidence does not support the efficacy of oral shark cartilage in cancer treatment. In a trial of 60 patients with various advanced cancers (59 patients refractory to conventional treatment and 1 patient who declined conventional treatment), disease progression was similar to historical controls, and quality of life did not improve overall (94). Preliminary results from three other small uncontrolled trials of patients with advanced cancers refractory to conventional therapy also failed to support efficacy (95, 96). One study of 22 patients with refractory renal-cell carcinoma compared outcomes for two different doses of shark cartilage. Median survival was significantly increased in the higher-dose group; however, group assignment was not randomized, and there was no control group of patients not taking shark cartilage. The results are, therefore, difficult to interpret (97). All studies described here were restricted to advanced cases in which conventional treatment had failed; shark cartilage might possibly be more effective at earlier stages of disease (98). Three RCTs of shark cartilage are under way (**Appendix Tables** 1 and 3).

In general, oral shark cartilage seems to be well tolerated. The most common adverse effects are gastrointestinal (94–97, 99). One study noted possible allergic reactions (99). A typical daily dose (70 g) of shark cartilage contains approximately 14 g of calcium, and recurrent hypercalcemia has been reported in two patients with a history of previous episodes (95, 100). Concerns have also been raised about potential adverse effects of angiogenesis inhibition in certain situations, such as surgery, vascular insufficiency (including coronary artery disease), pregnancy, and childhood (101, 102). No interactions with conventional radiation therapy or chemotherapy have been reported.

Despite the popularity of shark cartilage, there is currently insufficient evidence to support its efficacy in cancer treatment. However, adverse effects generally seem to be minor. Until the ongoing clinical trials provide further evidence, it seems reasonable for physicians to accept the use of shark cartilage in the absence of specific contraindications. It seems prudent to discourage the use of shark cartilage in patients with a history of hypercalcemia and in situations where angiogenesis inhibition might be harmful.

Acupuncture

A National Institutes of Health (NIH) Consensus Conference concluded that clear evidence supports efficacy of acupuncture in the control of chemotherapy-related nausea and vomiting (103). Six RCTs (five with placebo controls; only two with >50 patients) suggest that stimulation at P6 (a specific point proximal to the wrist), either alone or in conjunction with stimulation at ST36 (another point on the lower leg), serves as an effective adjunct to standard antiemetic medication (104–109). These findings are consistent with a larger body of data supporting the efficacy of various methods of P6 stimulation in the control of postoperative nausea and vomiting (110).

Another potential role of acupuncture in patients with cancer is the palliation of chronic pain. Several case reports and series suggest that acupuncture may provide relief when conventional measures fail to control chronic pain resulting from underlying disease or conventional treatments (surgery or radiation) (111–118). However, RCTs are needed to confirm the value of acupuncture in the management of chronic cancer-related pain.

The NIH Consensus Conference concluded that the overall frequency of acupuncture-related adverse events is extremely low (103), and prospective studies have indicated that even minor adverse events are rare (119). Treatment of nausea can be limited to a single specific point proximal to the wrist (in some cases combined with a second point on the leg). Unlike treatment of nausea, treatment of pain may require needle insertion at a wide variety of points, some of which overlie organs and nerves. Although case reports have described serious adverse events (such as pneumothorax), such incidents are very unlikely when a competent practitioner uses accepted techniques (119–121). However, it seems prudent to avoid insertion of acupuncture needles in patients who are thrombocytopenic or who are receiving anticoagulant therapy.

In summary, RCTs to date, although limited in size, suggest that it is certainly reasonable to accept the use of acupuncture in conjunction with standard antiemetics to control chemotherapy-related nausea and vomiting and that recommendation for this purpose might be considered. Fewer data are available on the use of acupuncture in palliation of chronic cancer-related pain, but it seems reasonable to accept this approach if patients elect to try it.

Massage

Few studies have evaluated massage in patients with cancer. Two small RCTs indicate that massage may reduce anxiety (122, 123). For relief of cancer-related pain, data are inconclusive; only one of three RCTs (ranging in size from 34 to 103 patients) found significant benefits for massage (122, 124, 125). However, these trials provided standardized massages; none attempted to direct treatment toward areas where individual patients experienced pain. Finally, one small RCT found that massage reduced nausea in patients undergoing autologous bone marrow transplantation (122).

Manual lymph drainage is a specialized form of massage used in patients with lymphedema. Two small trials (one randomized and one quasi-randomized) found manual lymph drainage to be an effective adjunct to compression bandaging or sleeves in patients with arm lymphedema after surgery for breast cancer (126, 127).

Currently, no evidence indicates that massage promotes tumor metastasis. However, it seems prudent to avoid massage directly over known tumors or even predictable metastasis sites without known disease (128). Particular caution should be exercised in patients with bony metastases, who may be prone to fracture.

Several other considerations are relevant for certain patients. Care must be taken to avoid further injury to tissues damaged by surgery or radiation therapy (128). Caution must be used in patients who are prone to bleeding (those who are thrombocytopenic or are receiving anticoagulant therapy). These patients may develop hematomas from pressures that would normally have no adverse effects (129). Deep abdominal massage has been associated with internal bleeding, even in the absence of coagulation abnormalities (130), and should be avoided in hypocoagulable patients. Hypercoagulability may also lead to problems because strong pressure over a thrombus can cause embolization (131); massage should be avoided over known thrombi (128). Finally, massage should be avoided over stents or other prosthetic devices because displacement can occur (132).

If the described precautions are observed, available evidence suggests that it is reasonable for physicians to accept the use of massage for relief of anxiety and as adjunct therapy for lymphedema and that physicians might consider recommending massage for these purposes. Although evidence on the benefits of massage for relief of cancer-related pain remains inconclusive, it seems reasonable to accept this approach if patients elect to try it.

Exercise

Although conventional medicine recognizes various health-related benefits of exercise, exercise regimens have not yet become standard adjuncts to conventional cancer therapy. **Appendix Tables 6** and 7 (available at www.annals.org) summarize trials assessing potential benefits of exercise in patients undergoing conventional treatment.

Psychological and Mind–Body Therapies

Examples of psychological and mind–body therapies include various forms of individual and group therapy, relaxation, imagery, hypnosis, and meditation. Several RCTs suggest that such interventions may alleviate emotional distress in patients with cancer (133–145). There is also some evidence that psychological and mind–body approaches may alleviate certain physical symptoms of disease and side effects of conventional treatment. For example, several RCTs support the efficacy of these approaches for alleviating cancer-related pain (142, 146–149). Because palliative applications of psychological and mind–body interventions have gained a certain level of acceptance in the conventional realm, use of these interventions for palliative purposes will not be discussed further.

A more controversial question is whether psychological and mind–body interventions enhance survival. Proposed mechanisms through which these interventions might increase survival in patients with cancer include improvement in immune function and beneficial behavioral change (**Appendix Table 8**, available at www.annals.org). Trials completed to date have yielded mixed results. Four studies (three randomized [150–152] and one quasi-randomized [153]) found significant survival benefits for such interventions, and an additional RCT showed a borderline significant increase in survival (154, 155). However, five other RCTs failed to find survival benefits (133, 142, 156–158), and an RCT evaluating response to chemotherapy rather than actual survival also failed to find benefits (137, 159). Most of the studies in both groups—trials that support survival benefits and trials that do not—have potential problems that may affect interpretation of results. Considering the limitations of the studies to date and their inconsistent results, conclusions on survival benefits of psychological and mind–body interventions remain premature.

For now, it seems reasonable to accept the use of psychological and mind–body interventions by patients who believe these techniques can extend survival. However, unrealistic expectations should not be encouraged. Physicians may guide patients toward realistic expectations for these interventions by explaining that, although survival benefits are uncertain, there are other potential benefits in terms of emotional state and physical symptoms.

CAM Supplements in Cancer: Major Categories of Adverse Effects and Interactions with Conventional Treatments

Anticoagulant Effects

Appendix Table 9 (available at www.annals.org) lists commonly used supplements with potential anticoagulant effects. Such supplements should be avoided by patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are in the perioperative period.

Phytoestrogenic Effects

Current data on soy suggest that it is prudent to discourage phytoestrogen supplementation in women with breast cancer (especially those who have estrogen receptor–positive tumors or who are taking tamoxifen) or endometrial cancer. In addition to soy supplements, several phytoestrogenic herbal products are commercially available. Some versions of Essiac (an herbal mixture commonly used by patients with cancer) contain the phytoestrogenic ingredient red clover (160–162). Furthermore, some herbs used in the broader population contain phytoestrogens. Evidence indicates that phytoestrogens are present in some preparations of ginseng, which is among the most popular herbs on the market today. Preclinical studies of various ginseng extracts have produced conflicting data about estrogenicity and about the effects of these extracts on the growth of breast cancer cells (163–165). However, case reports indicate that clinically significant estrogenic effects have occurred with commercially available products (165, 166). Finally, as noted earlier, some versions of the macrobiotic diet are high in phytoestrogens (16).

Alteration of Levels of Conventional Drugs

Supplements may alter blood levels of conventional medications through effects on metabolism. The popular herb St. John's wort, an inducer of the cytochrome P450 enzyme system and drug-transporting P-glycoprotein, reduces levels of various drugs (for example, cyclosporine and indinavir) (167–169). A recent RCT found that concomitant administration of St. John's wort significantly reduces levels of the active metabolite of the chemotherapeutic agent irinotecan (169). It seems prudent to avoid combining St. John's wort with chemotherapeutic agents or other drugs for which failure to achieve therapeutic levels could lead to serious consequences. Future research will likely identify numerous supplements that increase or decrease drug levels. Dietary changes (for example, consuming grapefruit juice) may also alter drug levels (170). As noted, limited data suggest that macrobiotic diets may affect metabolism of some drugs (19).

Interaction of Antioxidants with Radiation and Chemotherapy

Free radicals and reactive oxygen species mediate antitumor activity as well as adverse effects of some conventional agents. Antioxidants may limit adverse effects but could also theoretically diminish antitumor efficacy (171–173). Our discussion focuses on evidence regarding alterations in efficacy of conventional treatments by concurrent administration of antioxidants, and it is restricted to antioxidants that have not been approved for use with conventional treatments.

Because the generation of free radicals is central to the cytotoxic effects of radiation, the theoretical risk that antioxidants might diminish efficacy of radiation therapy is particularly high (171, 174). In addition, certain chemotherapeutic agents may rely on free radicals and reactive oxygen species as mediators of cytotoxicity (**Appendix Table 10**, available at www.annals.org); these agents must also be considered at high risk for potential inhibition by antioxidants (172). Studies that have tested the combination of nonprescription antioxidants with these "high-risk" conventional therapies have yielded mixed results. Most RCTs have not demonstrated significant differences in efficacy with concurrent antioxidant administration. One RCT combined radiation therapy with chemotherapy (175), one RCT used radiation therapy as the sole conventional therapy (173, 176), and five RCTs used chemotherapy regimens incorporating "high-risk" agents (177–181). However, some studies have reported either potentiation or inhibition of "high-risk" conventional therapies by antioxidants. In three RCTs, the antioxidant melatonin seemed to enhance the efficacy of radiation therapy (182) as well as some regimens incorporating "high-risk" chemotherapeutic agents (183, 184). Conversely, one RCT suggested inhibition of "high-risk" chemotherapeutic agents by an antioxidant (vitamin B_6) (185). Although no RCTs have yet shown inhibition of radiation efficacy by antioxidants, inhibition has been noted in two animal studies (186, 187). Of particular note, animal data suggest that a single antioxidant may cause either potentiation or inhibition, depending on dosage and timing of administration relative to irradiation (186, 188).

Certain chemotherapeutic agents do not seem to depend on free radicals and reactive oxygen species for therapeutic efficacy (**Appendix Table 10**, available at www.annals.org). These agents might be considered theoretically at low risk for potential inhibition by antioxidants (172). However, unexpected interactions may nonetheless result in either potentiation or inhibition of these "low-risk" agents. For example, the effects of 5-fluorouracil were enhanced by vitamin E in one animal study (189) and inhibited by β-carotene in another (190).

Three factors may complicate attempts to predict interactions between antioxidants and conventional therapies. First, individual antioxidants have unique properties in addition to their general antioxidant activity. Such properties could result in either potentiation or inhibition of conventional treatments. Elsewhere in this paper, we discuss individual effects of several antioxidants (the antioxidant vitamins and the isoflavonoids in soy protein). A second point is that uptake of certain antioxidants may vary among cell types (191, 192). However, no formula is available for determining which antioxidants are likely to be taken up by various types of malignant cells. Finally, our understanding of the cytotoxic mechanisms of chemotherapeutic agents is incomplete. Even if a specific agent is known to generate free radicals, it is not always clear that these radicals play an essential role in antitumor activity (193).

In summary, the limited data to date suggest that concurrent administration of antioxidants may result in either potentiation or inhibition of radiation therapy and chemotherapy. The outcome of any given pairing of an antioxidant with a conventional regimen is difficult to predict from theoretical models. Future studies will probably identify specific antioxidants that may be used in certain cancers to reduce toxicity of particular conventional agents without diminishing efficacy. Two antioxidants, dexrazoxane and amifostine, have already been approved to limit toxicity of specified regimens in certain patient populations (194). However, at this time, it is clear that antioxidants can reduce efficacy of conventional treatments in some cases, and it seems prudent to discourage concurrent use of nonprescription antioxidants with radiation therapy or chemotherapy until more evidence becomes available.

CURRENT TRIALS OF CAM THERAPIES IN PATIENTS WITH CANCER

Appendix Table 3 (available at www.annals.org) presents federally funded RCTs, and **Appendix Table 1** lists RCTs with nonfederal sponsors.

DISCUSSING CAM THERAPIES WITH PATIENTS WHO HAVE CANCER

When a patient with cancer seeks CAM therapy, the physician has an obligation to provide evidence-based advice in a manner that shows respect for the patient's beliefs and choices. Although the discussion will vary according to individual patient concerns, we believe that the following strategy will serve as a useful guide.

Table 4. **Complementary and Alternative Medical Therapies That May Reasonably Be Accepted and, in Some Cases, Considered for Recommendation***

- Certain dietary regimens (see text for information on dietary fat reduction in patients with breast or prostate cancer and on macrobiotic diets)
- Vitamin E supplementation
- Soy supplementation in prostate cancer
- Certain herbal products and biological agents (see text for information on shark cartilage)
- Acupuncture for chemotherapy-related nausea and vomiting or for pain
- Massage for anxiety or pain
- Moderate exercise
- Psychological and mind–body therapies (e.g., support groups, relaxation training, imagery)

* See Tables 2 and 3 in addition to the text for contraindications to the use of particular therapies in specific groups of patients.

Table 5. **Specific Complementary and Alternative Medical Therapies To Discourage and Avoid**

Therapy	Situation in Which It Is Prudent To Avoid Therapy
Highly restrictive dietary regimens	Poor nutritional status
Antioxidants	Concurrent radiation or chemotherapy
Supplements with anticoagulant effects	Thrombocytopenia, anticoagulant therapy, surgery
Phytoestrogens	Breast cancer (especially in the case of estrogen receptor–positive tumors or tamoxifen therapy), endometrial cancer
Acupuncture	Thrombocytopenia, anticoagulant therapy
Deep-tissue or forceful massage	Thrombocytopenia, anticoagulant therapy
St. John's wort	Concurrent chemotherapy or use of other drugs for which failure to achieve therapeutic levels could lead to serious consequences
High-dose vitamin A	Prudent for all patients to avoid
High-dose vitamin C	Prudent for all patients to avoid

The physician may begin by explaining that CAM therapies offer no "magic bullets" and that current evidence supporting CAM is stronger for alleviation of cancer-related symptoms than for slowing of disease progression. The physician might then summarize the CAM therapies he or she believes it would be reasonable to accept as part of the patient's care (**Tables 2** to **4**).

Several general cautions may be presented before discussing specific CAM therapies it seems prudent to avoid. The physician should discourage any intervention that delays conventional treatments of proven efficacy, treatment by unlicensed professionals, and the injection of substances not approved by the FDA. The patient should be informed that "natural" does not necessarily mean "safe" and that current labeling regulations do not ensure that what is found in the bottle corresponds to what is on the label (203). The physician should explain that because current evidence is inadequate to predict which supplements may increase or diminish the effects of radiation therapy or chemotherapy, it seems prudent to avoid combining these interventions until more information becomes available. Aside from these general cautions, there are many specific CAM therapies it seems prudent to avoid in certain situations and others that it seems prudent to avoid in all patients. The therapies we have reviewed that fall into these categories are summarized in **Table 5** (also see **Tables 2** and **3**).

When a patient decides to use a therapy, close follow-up by the physician is essential, regardless of the physician's advice about that therapy. The physician should remain alert for signs of adverse effects or interactions with conventional treatments. When a CAM (or conventional) therapy is started, use of a symptom diary may help determine whether the therapy is beneficial for the individual patient (204).

CONCLUSION

Several CAM therapies offer potential benefits for patients with cancer. Others, however, seem to be ineffective, and many present risks for direct adverse effects or interactions with conventional treatments. Therefore, it is important for physicians to communicate openly with patients about CAM use. Current evidence, although limited, suggests that physicians may reasonably accept some CAM therapies as adjuncts to conventional care and discourage others. As more data are gathered, the evidence-based recommendation of some CAM therapies and the evidence-based rejection of others will become more definitive.

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Effects of Subclinical Thyroid Dysfunction on the Heart

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Background: Mounting evidence indicates that subclinical thyroid dysfunction has important clinical effects and prognostic implications, supporting the view that it is not a compensated biochemical change sensu strictu.

Purpose: To review clinical information on the effects of subclinical thyroid dysfunction on the heart.

Data Sources: English-language articles identified from files and a MEDLINE search (1970–September 2001), references of relevant articles, textbooks, and meeting abstracts.

Study Selection: Reports on the effects of subclinical hypothyroidism and subclinical hyperthyroidism on the cardiovascular system in humans.

Data Extraction: Data on cardiac structure and performance, arrhythmias, and risk for coronary artery disease were independently assessed by all authors and summarized.

Data Synthesis: Subclinical hypothyroidism is associated with impaired left ventricular diastolic function at rest, systolic dysfunction on effort, and enhanced risk for atherosclerosis and myocardial infarction. Subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased left ventricular mass with marginal concentric remodeling, impaired ventricular relaxation, reduced exercise performance, and increased risk for cardiovascular death. All abnormalities were reversed by restoration of euthyroidism (subclinical hypothyroidism) or were blunted by β-blockade and tailoring of the L-thyroxine dose (subclinical hyperthyroidism).

Conclusion: The heart responds to the minimal but persistent changes in circulating thyroid hormone levels typical of subclinical thyroid dysfunction. Thus, the condition is not a compensated biochemical change sensu strictu, and timely treatment should be considered in an attempt to avoid adverse cardiovascular effects.

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The cardiovascular system is very sensitive to thyroid hormone, and a wide spectrum of cardiac changes has long been recognized in overt thyroid dysfunction (1–5). In contrast, cardiovascular impairment in patients with subclinical thyroid dysfunction has only recently been studied in detail (6–9). This condition, characterized by normal levels of circulating free thyroxine (FT_4) and free triiodothyronine (FT_3) and elevated (subclinical hypothyroidism) or below-normal (subclinical hyperthyroidism) thyroid-stimulating hormone (TSH) concentrations, is associated with changes in several cardiovascular measures. These changes support the view that subclinical thyroid dysfunction is not a compensated biochemical change sensu strictu. To clarify this process, we reviewed clinical studies of the consequences of subclinical thyroid dysfunction on the heart.

METHODS

Data sources were articles in our collection about the cardiovascular effects of subclinical thyroid dysfunction in humans published between 1970 and September 2001. We checked that articles had not been overlooked by searching the MEDLINE database (keywords were *thyroid hormone, heart, subclinical hypothyroidism, subclinical hyperthyroidism,* and *cardiovascular risk*), references of relevant articles, textbooks, and abstracts of presentations at international thyroid meetings. Given the relatively few studies on the effect of subclinical thyroid disease on the cardiovascular system, we are confident that we considered all English-language peer-reviewed reports. All authors assessed the reports and agreed about article content.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism, defined as increased serum TSH concentrations associated with normal FT_4 and FT_3 concentrations, may be caused by exogenous (L-thyroxine under-replacement in hypothyroid patients; medication with lithium, cytokines, iodine, or antithyroid drugs; and iodine 131 therapy or thyroidectomy) or endogenous (Hashimoto thyroiditis and previous subacute or silent thyroiditis) factors (8). Its prevalence ranges from 1.3% to 17.5%, depending on age, sex, and iodine intake (10–14). A large cross-sectional study from Colorado reported a mean prevalence of 9% (15). People with thyroid antibodies caused by Hashimoto thyroiditis are prone to subclinical hypothyroidism. The incidence of subclinical hypothyroidism, derived from a review (14) of three longitudinal studies that included a total of 2956 patients (with 6-, 10-, and 20-year follow-up, respectively) (16–18), is 2.1% to 3.8% per year in thyroid antibody–positive patients and about 0.3% per year in thyroid antibody–negative patients. The annual risk for developing overt hypothyroidism after 20 years is 4.3% in women with increased TSH concentrations and thyroid antibodies and 2.6% in women with subclinical hypothyroidism without thyroid antibodies (18).

Cardiac Manifestations

Table 1 lists the cardiovascular abnormalities reported in subclinical hypothyroidism (19–33). Resting heart rate was normal in all patients in whom it was evaluated (21, 22, 25, 28–30, 33). Cardiac function, evaluated from systolic time intervals, was also normal in patients with subclinical hypothyroidism (19, 27). In contrast, the preejec-

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Table 1. **Cardiovascular Abnormalities in Subclinical Hypothyroidism***

Study, Year (Reference)	Patients, *n*	Mean TSH Concentration ± SD, *mU/L*	Method	Heart Rate	LV Mass	LV Systolic Function	LV Diastolic Function	Exercise Performance
Bough et al., 1978 (19)	10	13.1 ± 1.1	STI	–	–	↔ PEP, ↔ LVET, ↔ PEP/LVET	–	–
Ridgway et al., 1981 (20)	20	28 ± 6	STI	–	–	↑ PEP, ↑ PEP/LVET, ↑ QKd	–	–
Cooper et al., 1984 (21)	17	10.8 ± 2.2	STI	↔	–	↑ PEP/LVET	–	–
Bell et al., 1985 (22)	18	17.9 ± 2.4	RNV	↔	–	↔ Ejection fraction	–	↓ Ejection fraction
Forfar et al., 1985 (23)	10	–	RNV	–	–	↔ Ejection fraction	–	↓ Ejection fraction
Földes et al., 1987 (24)	17	10.31 ± 1.54	STI, RNV	–	–	↔ PEP, ↓ ejection fraction, ↔ cardiac output, ↔ stroke index	–	↓ Ejection fraction
Nyström et al., 1988 (25)	17	7.7 ± 0.9	STI	↔	–	↑ PEP, ↑ PEP/LVET	–	–
Tseng et al., 1989 (26)	22	10.7 ± 2.2	Echo	–	–	↔ PEP, ↔ PEP/LVET	–	–
Staub et al., 1992 (27)	14	8.6 ± 0.5	STI	–	–	↔ PEP, ↔ PEP/LVET	–	–
Arem et al., 1996 (28)	8	14.8 ± 3.3	Doppler echo	↔	–	↔ Fractional shortening, ↔ ejection fraction	↔ E/A, ↓ LVEDD	↑ PEP
Biondi et al., 1999 (29)	26	8.6 ± 0.9	Doppler echo	↔	↔	↔ Fractional shortening, ↔ VCF, ↓ aortic acceleration	↓ E/A, ↑ IVRT	–
Di Bello et al., 2000 (30)	16	5.27 ± 0.47	Doppler echo	↔	↔	↔ Fractional shortening, ↔ cardiac output, ↑ PEP, ↑ PEP/LVET	↑ A, ↔ E/A, ↑ IVRT	–
Kahaly, 2000 (31)	20	11.2 (6.3–19.5)	Doppler echo, CPEx	–	–	↔	–	↓ Stroke volume, ↓ cardiac output, ↑ PEP, ↓ aortic flow velocity, ↓ anaerobic threshold (Watt)
Brenta et al., 2000 (32)	10	11.0 ± 1.4	RNV	–	–	–	↑ TPFR	–
Monzani et al., 2001 (33)	20	~5.1 ± 0.6	Doppler echo	↔	↑	↔ Fractional shortening, ↑ PEP, ↑ PEP/LVET, ↔ cardiac output	↑ A, ↑ IVRT	–

* ↑ = increased; ↓ = decreased; ↔ = unchanged; A = late transmitral peak flow velocity; CPEx = cardiopulmonary exercise testing; E/A = early to late transmitral peak flow velocity ratio; echo = echocardiography; IVRT = isovolumic relaxation time; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVET = left ventricular ejection time; PEP = preejection period; QKd = the interval from Q wave on the electrocardiogram to the pulse arrival time at the brachial artery; RNV = radionuclide ventriculography; STI = systolic time intervals; TPFR = time to peak filling rate; TSH = thyroid-stimulating hormone; VCF = velocity of circumferential fiber shortening.

tion period and the interval from Q wave to pulse arrival at the brachial artery were prolonged, and the preejection period–left ventricular ejection time ratio was higher in 20 patients with subclinical hypothyroidism than in the same patients after L-thyroxine replacement therapy (20).

In the first double-blind study of the effects of 1 year of L-thyroxine therapy compared with placebo in 17 patients with subclinical hypothyroidism of different origins, the preejection period–left ventricular ejection time ratio was significantly decreased after L-thyroxine therapy, particularly in patients with the highest ratio (>0.390) (21). In 18 patients, L-thyroxine caused a small but significant increase in left ventricular ejection fraction (evaluated by radionuclide ventriculography) during maximal exercise but caused no change at rest or during moderate exercise (22).

In 10 patients evaluated before and after TSH concentrations were normalized with L-thyroxine, the treatment did not affect left ventricular ejection fraction at rest but did enhance the increase in ejection fraction during exercise (23). In the same study, sodium nitroprusside produced similar increases in cardiac output in patients with subclinical hypothyroidism and in euthyroid persons. However, in the former group, enhanced cardiac output was due to a large increase in heart rate and reduced stroke volume, whereas euthyroid persons had a smaller increase in heart rate and no change in stroke volume. Therefore, restoration of euthyroidism by L-thyroxine improves systolic function on effort in patients with subclinical hypothyroidism. This could have resulted from improved myocardial contractility and, perhaps, lusitropic function. The preejection period was prolonged in only 5 of 17 patients with subclinical hypothyroidism compared with 50 euthyroid controls, whereas the mean left ventricular ejection fraction was reduced both at rest and during isometric exercise (24).

In the first double-blind, crossover study of women with subclinical hypothyroidism due to Hashimoto thyroiditis, 20 randomly selected women with primary subclinical hypothyroidism received L-thyroxine and placebo for 6 months each (25). Left ventricular systolic function was assessed from systolic time intervals before and after L-thyroxine. Heart rate–corrected preejection period and the preejection period–left ventricular ejection time ratio decreased significantly after treatment. In another study, left ventricular function, evaluated by echocardiography-derived systolic time intervals, was unchanged in 22 patients with subclinical hypothyroidism compared with normal controls (26).

In eight subclinical hypothyroid patients evaluated at rest and during bicycle-ergometer exercise testing before and after L-thyroxine treatment, Doppler-derived systolic time intervals showed a more prolonged preejection period and a higher preejection period–left ventricular ejection time ratio during pretreatment maximum exercise (28). Echocardiographic left ventricular end-diastolic dimension was slightly but significantly lower before L-thyroxine treatment.

Left ventricular structure and function at rest were evaluated by using Doppler echocardiography in 26 selected patients with stable subclinical hypothyroidism due to Hashimoto thyroiditis and in 30 normal controls (29). In 10 randomly selected patients, the evaluation was repeated after 6 months of L-thyroxine therapy (daily dose, 68 μg). No significant abnormality in left ventricular structure was seen, whereas Doppler-derived mean aortic acceleration, a reliable index of left ventricular systolic function, was significantly lower in patients than in controls. This acceleration normalized after L-thyroxine therapy. Furthermore, isovolumic relaxation time was prolonged, and the early–late ratio of Doppler-derived transmitral peak flow velocities was lower in patients than in controls. Both measures of diastolic function returned to normal after L-thyroxine replacement. Doppler echocardiography and ultrasonic myocardial textural analysis confirmed these findings in 16 patients with subclinical hypothyroidism (30). They had a significantly increased left ventricular mass and lower cyclic variation measures (percentage systolic/diastolic change in mean gray levels) in both the interventricular septum and the left ventricular posterior wall (30).

Radionuclide ventriculography revealed a longer time to peak filling rate in 10 patients with subclinical hypothyroidism than in 10 normal controls (32). This index of diastolic function normalized after L-thyroxine replacement. Using stress Doppler echocardiography and cardiopulmonary exercise testing, Kahaly (31) studied 20 patients with subclinical hypothyroidism before and after L-thyroxine therapy and 20 normal controls. At rest, the cardiac measures recorded in untreated patients approximated those obtained in controls and in euthyroid patients. However, patients had significantly lower stroke volume, cardiac index, and peak aortic flow velocity and significantly prolonged preejection period during exercise. All measures normalized after a euthyroid state was achieved. Furthermore, the oxygen pulse (oxygen uptake per heartbeat), an index of stroke volume, was significantly decreased both at the anaerobic threshold and at maximal work capacity, and work rate was reduced at the anaerobic threshold in patients versus controls. These measures normalized after replacement therapy.

Finally, in a double-blind, placebo-controlled study of the effects of L-thyroxine replacement therapy on cardiac structure and function in subclinical hypothyroidism, cardiac measures, evaluated by Doppler echocardiography and videodensitometry, were almost normal after L-thyroxine therapy (33).

Coronary Artery Disease

Overt hypothyroidism increases serum cholesterol levels (15, 27, 34–36), but it is not known whether subclinical hypothyroidism affects serum lipid profiles. Serum cholesterol levels have been significantly higher in patients with subclinical hypothyroidism than in normal controls (31, 37–40). In other studies, levels were only marginally increased (41–43). In three studies, the prevalence of subclinical or overt hypothyroidism was higher in hypercholesterolemic patients (44–46), a finding not confirmed in a subsequent study (47). Other markers of atherosclerotic risk described in overt hypothyroidism (enhanced low-density lipoprotein oxidation, elevated lipoprotein(a) levels, and hyperhomocysteinemia) may also be responsible for an association between subclinical hypothyroidism and coronary artery disease (48–50). Of interest, a recent quantitative review of patients with subclinical hypothyroidism showed that restoration of euthyroidism by L-thyroxine reduced both total and low-density lipoprotein cholesterol levels. The reduction was more pronounced in patients with higher pretreatment cholesterol levels and TSH concentrations (51). Moreover, L-thyroxine significantly reduced lipoprotein(a) and homocysteine levels in patients with overt and subclinical hypothyroidism (52, 53).

Two studies have shown an association between subclinical hypothyroidism and coronary artery disease (54, 55), whereas others have either found no association or only a weak association between minor electrocardiographic changes and a minor degree of hypothyroidism in women (41, 56, 57). Striking evidence of a higher risk for atherosclerotic cardiovascular death in patients with subclinical hypothyroidism emerged from the Rotterdam study (58). This large epidemiologic study concluded that subclinical hypothyroidism is associated with a greater prevalence of aortic atherosclerosis and myocardial infarction in elderly women. Perk and O'Neill, using sequential coronary angiography, found that appropriate thyroid hormone replacement therapy prevented progression of angiographic coronary artery disease in hypothyroid patients (59).

Patients with subclinical hypothyroidism have abnormal vascular reactivity, which is identified by impaired flow-mediated, endothelium-dependent vasodilatation (31, 60, 61). The association between pathologic immune vascular damage due to thyroid autoimmunity and coronary artery disease is controversial (54–58, 62, 63). The two largest epidemiologic studies that addressed this issue did not identify an association between autoimmune thyroid disease and mortality or development of coronary artery disease (58, 63). This finding weakens the hypothesis that pathologic immune vascular damage may be an important factor in the association of autoimmune thyroiditis with coronary artery disease, independently of whether the TSH concentration is normal or increased.

Commentary

The results of studies on the effects of subclinical hypothyroidism on left ventricular structure and function are controversial, particularly with regard to the effects on left ventricular systolic function at rest. Conflicting results might be related to a less than rigorous selection of patients (enrollment of patients with previous hyperthyroidism or with acute or unstable subclinical hypothyroidism) and to different diagnostic criteria for subclinical hypothyroidism (a wide range of TSH concentrations) (19–24, 26–28). Indeed, in many early studies, inclusion of patients with previous overt hyperthyroidism could have confounded the evaluation of left ventricular structure and function. In other studies, the cardiac measures obtained during the subclinical hypothyroid state were compared with those obtained in the same patients after L-thyroxine replacement therapy. However, thyroid hormone could itself affect the heart independently of the underlying thyroid disease. Nevertheless, studies have clearly shown that patients with subclinical hypothyroidism have impaired left ventricular diastolic function at rest and systolic dysfunction on effort, which may result in poor physical exercise capacity. Moreover, resting left ventricular diastolic dysfunction is often the first manifestation of heart disease, even preceding systolic dysfunction at rest (64, 65). Altered serum lipid levels and abnormal vascular reactivity in patients with subclinical hypothyroidism, particularly in elderly women, may confer a higher risk for cardiovascular disease. Therefore, subclinical hypothyroidism should be considered a mild form of thyroid failure sensu strictu that is associated with initial signs of cardiovascular hypothyroidism.

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism, characterized by low or undetectable serum TSH concentrations and normal FT_4 and FT_3 concentrations, may be caused by exogenous and endogenous factors (9, 66). The major exogenous cause is the use of L-thyroxine to suppress TSH in patients with thyroid nodular disease or to prevent local or metastatic progression of differentiated thyroid carcinoma after surgery (9, 66). Overzealous hormone replacement therapy; misunderstandings about prescriptions; and changes in L-thyroxine requirement, absorption, and formulation are additional potential causes (9, 15, 66–68). Like overt hyperthyroidism, endogenous subclinical hyperthyroidism is due to Graves disease, multinodular goiter, or an autonomously functioning thyroid nodule (9, 66). The prevalence of subclinical hyperthyroidism ranges from 0.6% to 16% (13, 14, 66), depending on the definition used (that is, TSH concentration lower than normal, <0.1 mU/L, or undetectable in a given assay), the sensitivity of the method used to measure TSH concentrations, and iodine intake in the study sample. The exogenous form of subclinical hyperthyroidism is the most prevalent (15); the endogenous form is frequent in geographic areas with iodine insufficiency (69, 70).

Low or undetectable TSH concentrations are generally temporary in patients with Graves disease. Conversely, multinodular goiter or autonomously functioning thyroid nodules are characterized by prolonged periods of subclinical hyperthyroidism (71–73). Overt thyrotoxicosis is often precipitated by increased iodine intake after administration of iodine-containing drugs or radiographic contrast agents (74). Iodine-induced thyrotoxicosis can be secondary to iodine prophylaxis in populations with endemic goiter (75–77). Prospective studies of patients with endogenous subclinical hyperthyroidism (1 to 4 years of follow-up) showed that TSH concentrations increased spontaneously in almost 50% of cases (although the normal reference range was not always reached) and remained unchanged in 35%, whereas overt hyperthyroidism developed in 10% of patients at a rate of 5% per year (78–82).

Cardiac Manifestations

Given the pathophysiologic differences between exogenous and endogenous subclinical hyperthyroidism, we review cardiac manifestations of the two disorders separately (Table 2) (26, 83–96).

Exogenous Subclinical Hyperthyroidism

Bell and colleagues (83) first demonstrated the cardiac effects of exogenous subclinical hyperthyroidism. They studied 7 normal persons by using 24-hour Holter electrocardiography at baseline and after L-thyroxine administration, when the plasma TSH response to TSH-releasing hormone was inhibited. The mean nocturnal and mean daytime heart rate increased after treatment, the former significantly so. The first evidence of mild but significant changes in myocardial function was reported in 1984 in hypothyroid patients receiving over-replacement therapy with L-thyroxine and showing minimally elevated serum FT_4 concentrations and suppressed TSH (84). Systolic time intervals within the thyrotoxic range alerted the physician to tissue thyrotoxicosis and to the need to reduce the L-thyroxine dose. The mean preejection period–left ventricular ejection time ratio was lower than normal in 15 patients receiving replacement L-thyroxine therapy and increased in 7 patients after reduction of the L-thyroxine dose (84). Results were similar in 18 patients with exogenous subclinical hyperthyroidism (86).

Concurrent aortic and mitral valve echocardiographic tracing has revealed a significantly shorter isovolumic contraction time and preejection period and lower preejection

Table 2. **Cardiovascular Abnormalities in Subclinical Hyperthyroidism***

Study, Year (Reference)	Patients, *n*	Methods	Cause	Heart Rate	LV Mass	LV Systolic Function	LV Diastolic Function	Exercise Performance	Ventricular Arrhythmias	Supraventricular Arrhythmias
Bell et al., 1983 (83)	7	Holter ECG	Exogenous	↑	–	–	–	–	–	–
Jennings et al., 1984 (84)	15	STI	Exogenous	–	–	↓ PEP/LVET	–	–	–	–
Boutin et al., 1986 (85)	16	Pulse examination	Endogenous	↑	–	–	–	–	–	–
Banovac et al., 1989 (86)	18	STI	Exogenous	–	–	↓ PEP, ↓ PEP/LVET	–	–	–	–
Tseng et al., 1989 (26)	15	Echo	Exogenous	↔	–	↓ Isovolumic contraction time, ↓ PEP, ↓ PEP/LVET	–	–	–	–
Grund and Niewoehner, 1989 (87)	11	RNV	Exogenous	↑	–	↔ Ejection fraction	–	–	–	–
Biondi et al., 1993 (88)	20	Echo, Holter ECG	Exogenous	↑	↑	↑ VCF, ↑ fractional shortening	–	–	↔	↑
Fazio et al., 1995 (89)	25	Doppler echo	Exogenous	↑	↑	–	↑ IVRT, ↓ E/A	–	–	–
Biondi et al., 1996 (90)	10	RNV	Exogenous	↑	–	↔ Ejection fraction	↓ Peak filling rate	↓ Ejection fraction	–	–
Ching et al., 1996 (91)	11	Echo, Holter blood pressure	Exogenous	↔	↑	↔ Ejection fraction, ↔ fractional shortening	–	–	–	–
Shapiro et al., 1997 (92)	17	Doppler echo, Holter ECG	Exogenous	↔	↑	↔ Ejection fraction	↔ E/A	–	↔	↔
Biondi et al., 1999 (93)	60	Doppler echo, Holter ECG	Exogenous	↑	↑	↑ Fractional shortening, ↑ VCF	↑ IVRT, ↓ E/A	–	↔	↑
Mercuro et al., 2000 (94)	19	Doppler echo, CPEx	Exogenous	↔	↑	↔ Ejection fraction	↑ IVRT, ↔ E/A	↓ Peak Watt, ↓ VO_2 max, ↓ VO_2 anaerobic threshold	–	–
Biondi et al., 2000 (95)	23	Doppler echo, Holter ECG	Endogenous	↑	↑	↑ Fractional shortening, ↑ VCF, ↑ aortic acceleration	↑ IVRT, ↓ E/A	–	↔	↔
Sgarbi et al., 2000 (96)	10	Doppler echo, Holter ECG	Endogenous	↑	↑	↑ VCF	–	–	↑	↑

* ↑ = increased; ↓ = decreased; ↔ = unchanged; CPEx = cardiopulmonary exercise testing; E/A = early to late transmitral peak flow velocity ratio; ECG = electrocardiography; echo = echocardiography; IVRT = isovolumic relaxation time; LV = left ventricular; LVET = left ventricular ejection time; PEP = preejection period; RNV = radionuclide ventriculography; STI = systolic time intervals; VCF = velocity of circumferential fiber shortening; VO_2 = oxygen uptake.

period–left ventricular ejection time ratios in patients with exogenous subclinical hyperthyroidism (26). Eleven patients with an elevated FT_4 index and suppressed TSH due to L-thyroxine over-replacement therapy were evaluated by using resting radionuclide ventriculography at baseline and after the daily L-thyroxine dose was progressively reduced by 25 μg at 3-month intervals until normalization of the FT_4 index (87). Heart rate was significantly reduced by titration of the L-thyroxine dose, while left ventricular ejection fraction decreased nonsignificantly in 8 of 11 patients.

Echocardiography showed an increased left ventricular mass index in 20 patients with persistent exogenous subclinical hyperthyroidism (88). Left ventricular systolic function was also enhanced, as documented by the increase of fractional shortening and the rate-adjusted velocity of shortening. During a 24-hour period, the patients' heart rates, assessed by 24-hour Holter electrocardiography, were constantly higher than those of controls. Atrial premature beats were more frequent in patients than in controls: Two patients had atrial fibrillation. The prevalence of ventricular arrhythmias did not differ between groups (88). A subsequent study confirmed these results in a much larger group of patients (93).

The effects of 6-month β-blockade were evaluated in 11 patients with exogenous subclinical hyperthyroidism who were selected because of symptoms mimicking exaggerated β-adrenergic activity (97). This study showed a significant reduction in the average heart rate and the prevalence of atrial premature beats. After β-blockade, atrial fibrillation disappeared, left ventricular mass index was substantially reduced, and measures of left ventricular systolic function remained slightly enhanced.

Compared with normal controls, 25 patients receiving long-term TSH suppressive therapy evaluated with Doppler echocardiography had a significant increase in the left ventricular mass index accompanied by impaired indices of left ventricular diastolic function (prolonged isovolumic relaxation time and reduced ratio of early to late transmitral peak flow velocities) (89). Impaired left ventricular diastolic function was more evident in a subgroup of 10 patients who had greater adrenergic overactivity and higher left ventricular mass index values. In these 10 patients, 4 months of β-blockade significantly reduced cardiac hypertrophy, thereby improving left ventricular diastolic filling.

In 1996, Biondi and colleagues (90) investigated cardiac reserve and exercise capacity using radionuclide ventriculography in 10 patients receiving long-term L-thyroxine therapy who reported symptoms of adrenergic overactivity. Patients were evaluated before and after 4 months of β-blockade. Exercise capacity, assessed as peak workload and exercise duration, was markedly worse in patients than in controls. In addition, resting left ventricular diastolic filling was impaired and ejection fraction decreased during exercise. β-Adrenergic blockade reversed the decrease in ejection fraction and almost normalized resting diastolic function, which improved exercise tolerance.

Blood pressure, heart rate, left ventricular systolic function, autonomic function, forearm blood flow, and vascular resistance did not change in 11 patients with exogenous subclinical hyperthyroidism evaluated with 24-hour monitoring of pulse and blood pressure, echocardiography, forearm plethysmography, and autonomic function testing (91). However, patients had significantly higher left ventricular mass index values than did controls.

L-Thyroxine treatment did not affect left ventricular systolic and diastolic function in 17 patients with subclinical hyperthyroidism evaluated by using Doppler echocardiography and 24-hour Holter electrocardiography (92), but the mean left ventricular mass index was significantly higher in patients than in controls. Mean heart rate and the prevalence of atrial or ventricular premature contractions did not change. However, patients taking β-blocker drugs during L-thyroxine treatment were excluded from the evaluation.

Finally, Mercuro and colleagues (94) studied cardiac function and physical exercise capacity by using Doppler echocardiography and cardiopulmonary exercise testing in 19 patients receiving long-term TSH-suppressive treatment. The mean resting heart rate was marginally higher in patients than in controls. Doppler echocardiography showed significantly increased left ventricular mass in patients with subclinical hyperthyroidism accompanied by impaired left ventricular relaxation and preserved resting systolic function. Nine of the 19 patients had significantly reduced exercise performance, as shown by a significant reduction in peak workload, peak oxygen uptake, and anaerobic threshold. Of interest, noradrenaline concentrations at rest were significantly lower in TSH-suppressed patients when measured in both supine and standing positions. Individual tailoring of the TSH-suppressive L-thyroxine dose in 7 patients almost normalized all Doppler echocardiographic and cardiopulmonary exercise measures but did not alter noradrenaline concentrations. Reduced noradrenaline concentration in the patients with subclinical hyperthyroidism agrees with a report of lower noradrenaline levels in patients with overt thyrotoxicosis (98).

Endogenous Subclinical Hyperthyroidism

Only three studies have evaluated the effect of endogenous subclinical hyperthyroidism on the heart (85, 95, 96). In a pioneering investigation among participants with multinodular goiter, normal FT$_3$ and FT$_4$ concentrations, and a low TSH response to TSH-releasing hormone, Boutin and colleagues reported a higher pulse rate in patients than in controls (85). More recently, 23 patients with endogenous subclinical hyperthyroidism (15 affected by multinodular goiter and 8 by autonomously functioning thyroid nodule) were investigated by using 24-hour Holter electrocardiography and Doppler echocardiography (95). The average heart rate was significantly higher in patients than in normal persons. The prevalence of supraventricular and ventricular arrhythmias did not differ between the two groups. In the patients with subclinical hyperthyroidism, fractional shortening increased by about 14%, the heart rate–adjusted mean velocity of circumferential fiber shortening increased by about 7%, and peak aortic flow velocity increased by about 19%. Left ventricular mass was significantly higher in this group because of the increased thickness of both the interventricular septum and the posterior wall. These patients also had impaired diastolic function characterized by delayed relaxation.

Results were similar in 10 patients with endogenous subclinical hyperthyroidism (96). When these patients reached euthyroidism after 6 months of methimazole treatment, the mean 24-hour heart rate, atrial premature beats, and left ventricular mass had returned to normal.

Epidemiologic Evidence on Subclinical Hyperthyroidism and Atrial Fibrillation

Two longitudinal studies of older people have addressed atrial fibrillation in subclinical hyperthyroidism (82, 99). In 40 patients with subclinical hyperthyroidism (mean age, 65 years), Tenerz and colleagues (82) found 8 cases of atrial fibrillation, and 3 additional patients developed atrial fibrillation during the 2-year follow-up. The total rate of atrial fibrillation was 28% in patients compared with 10% in an age-matched group of euthyroid persons. In the Framingham study (99), 2007 participants 60 years of age or older with low TSH levels due to exogenous or endogenous factors had a threefold higher risk for atrial fibrillation. Studies of overt hyperthyroidism have shown that 10% to 15% of patients with atrial fibrillation may have an arterial embolic event (3, 6). Although there are no data on the incidence of arterial embolism due to atrial fibrillation in patients with subclinical hyperthyroidism, observations made in overt hyperthyroidism might apply to patients with subclinical hyperthyroidism.

Commentary

Exogenous and endogenous subclinical hyperthyroidism exert many relevant effects on the heart (82–97, 99). Results about resting heart rate in patients with subclinical hyperthyroidism are not consistent. Only four studies of exogenous subclinical hyperthyroidism (83, 88, 92, 93) and two studies of the endogenous condition (95, 96) assessed heart rate by using 24-hour Holter electrocardiography. The mean 24-hour heart rate was increased, also during nocturnal hours, in all these studies except one (93); that study had excluded patients with subclinical hyperthyroidism who were taking β-blockers. Increased exercise heart rate was reported in two studies, and, at a comparable workload, patients with exogenous subclinical hyperthyroidism had a higher heart rate than normal controls (90, 94). The prevalence and incidence of atrial fibrillation were higher in patients with subclinical hyperthyroidism 60 years of age or older (82, 99), whereas atrial premature beats were increased in some younger patients (88, 93, 96).

There is no consensus about the effects of subclinical hyperthyroidism on left ventricular function at rest. Systolic function has been reported to be increased (26, 84, 86, 88, 93, 95, 96) and unchanged (91, 92, 94). However, impaired left ventricular performance on exercise and decreased effort tolerance were found in the only two studies that evaluated cardiac performance and exercise capacity in patients with subclinical hyperthyroidism (90, 94). All the studies of cardiac structure in patients with subclinical hyperthyroidism showed an increased left ventricular mass with a tendency toward left ventricular concentric remodeling (88–96). This was sometimes accompanied by impaired ventricular relaxation (89, 90, 93–95) and decreased exercise performance (90, 94). The favorable effect promoted by thyroid hormone on diastolic performance (100, 101) may be counteracted by the adverse effect of myocardial hypertrophy on diastolic function (64, 65). These abnormalities were improved by β-blockade or by tailoring the L-thyroxine dose in patients with exogenous subclinical hyperthyroidism and by methimazole in patients with endogenous subclinical hyperthyroidism (89, 90, 94, 96). The prognostic significance of increased left ventricular mass in exogenous and endogenous subclinical hyperthyroidism is unclear because of the scarcity of epidemiologic studies on cardiovascular risk in these patients (99, 102). Patients with endogenous subclinical hyperthyroidism have been reported to have a higher rate of death from all causes, but especially from circulatory disease, than people with normal thyroid function (103). The mechanisms by which subclinical hyperthyroidism may increase mortality from cardiovascular disease are unknown. Although left ventricular mass in patients with subclinical hyperthyroidism is not sufficiently high to be classified as "left ventricular hypertrophy," an increase in left ventricular mass is more likely to be harmful than beneficial (104–106). Increased heart rate may also increase risk for cardiovascular and noncardiovascular death (107). Finally, because increased morbidity and mortality from thromboembolic events are associated with atrial fibrillation, subclinical hyperthyroidism in older patients may be considered a risk factor for thromboembolism.

GENERAL CONSIDERATIONS

Despite the high prevalence of subclinical thyroid dysfunction in the general population, treatment of this condition is controversial (66, 108–117). Our overview of the cardiovascular effects induced by subclinical hypothyroidism and subclinical hyperthyroidism shows that minimal but "persistent" changes in thyroid hormone levels, as occur in subclinical thyroid dysfunction, cause changes in the heart. Large epidemiologic studies have shown that, in elderly persons, subclinical hypothyroidism is associated with increased risk for atherosclerosis and coronary artery disease (58), whereas subclinical hyperthyroidism is associated with increased mortality from all causes, but especially from cardiovascular disease (103). Further research is needed to clarify better the intrinsic mechanisms by which subclinical thyroid dysfunction affects cardiovascular risk.

The data show that subclinical thyroid dysfunction is not a compensated biochemical state, and hence timely treatment could help to prevent cardiovascular involvement. An important observation to emerge from this review is that changes in cardiovascular measures can also be found in subclinical hypothyroid patients with TSH values less than 10 mU/L. According to the literature, "persistent" subclinical hypothyroidism with TSH values stably above 4.0 mU/L should be treated, particularly if associated with thyroid antibodies. The benefits of treatment are an improved lipid profile, possible reduced risk for atherosclerosis and coronary artery disease, prevention of cardiac morphologic and functional abnormalities and progression to overt hypothyroidism, a modest symptomatic benefit after L-thyroxine, and prevention of goiter in some patients. The L-thyroxine dose must be lower in patients with subclinical hypothyroidism than in those with overt disease (1.0 μg/kg of body weight vs. 2.0 μg/kg), and patients must be monitored until the optimal replacement dose is achieved. Young and middle-aged patients may start with 25 μg of L-thyroxine, with progressive increases in the dose until the TSH level ranges from 1 to 2 mU/L. If TSH concentrations remain normal, values may be checked every 6 to 12 months. In elderly patients with subclinical hypothyroidism, it is prudent to begin with a low dose of L-thyroxine (12.5 to 25 μg) and then titrate the dose upward at 4- to 6-week intervals on the basis of serial TSH determinations and clinical evaluation. Cardiac conditions should be assessed before initiating therapy to avoid exacerbation of ischemic heart disease. The target dose of L-thyroxine is lower in elderly patients than in young and middle-aged patients because of decreased thyroxine metabolism in the former group.

Because the most common cause of subclinical thyroid dysfunction is L-thyroxine therapy (15), periodic evaluations of serum TSH levels seem justified to ensure that replacement therapy is not under- or over-prescribed. Appropriate replacement therapy to maintain TSH levels in the normal range is necessary in hypothyroid patients to avoid the adverse cardiovascular effects of mild thyroid hormone excess or deficiency.

Given the increased mortality in patients with subclinical hyperthyroidism older than 60 years of age, subnormal TSH concentrations should be avoided in elderly patients (103, 117). Before surgery or iodine 131 therapy, elderly patients with subclinical hyperthyroidism should receive treatment with low doses of antithyroid drugs or β-blockers. However, the cardiovascular risk related to the increased left ventricular mass and to the deleterious effects of overt thyrotoxicosis in hearts previously exposed to prolonged subclinical hyperthyroidism should also be considered in younger patients (118).

L-thyroxine suppressive therapy must be carefully customized in patients with benign thyroid disease; TSH concentrations should be maintained at the low end of normal range, and treatment outcome should be assessed after 6 to 12 months of therapy. Long-term TSH suppressive therapy must be associated with periodic cardiovascular assessment. Cancer recurrence and mortality rate may be increased in patients with differentiated thyroid cancer who are inadequately treated with L-thyroxine (119). New guidelines for L-thyroxine therapy are needed for patients with the highest-risk tumors to maximize the benefit of therapy on thyroid cancer cell growth while avoiding the long-term adverse effects of TSH suppression. In the meantime, β-blockade may be considered in patients with adrenergic hyper-responsiveness to L-thyroxine, since it blunts the increase in heart rate, prevents the development of left ventricular hypertrophy, and effectively reduces the risk for supraventricular arrhythmias (89, 90, 93, 97).

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AD LIBITUM

Charleston Sunset

The same fire,
  which has lit
the edges of the world,
  feeds the glow inside of me
and I am standing
  with a handful of questions.
As I drop them,
  one by one,
you dip behind a boat
  to pick one from the pile at my feet:

How could you end this moment
  in any more splendor?

But, you stay tucked away,
  without a response,
no smoke, no suddenness,
  just a quiet dwindling of a gentle flame,
and, there I am,
  standing empty-handed,
with nothing else left to hold
. . .besides my breath.

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Screening for Prostate Cancer: Recommendation and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendations on screening for prostate cancer and updates the 1996 recommendations on this topic. The complete USPSTF recommendation and rationale statement on this topic, which includes a brief review of the supporting evidence, is available through the USPSTF Web site (www.preventiveservices.ahrq.gov), the National Guideline Clearinghouse (www.guideline.gov), and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (telephone, 800-358-9295; e-mail, ahrqpubs@ahrq.gov). The complete information on which this statement is based, including tables and references, is available in the accompanying article in this issue and in the summary of the evidence and systematic evidence review on the Web sites already mentioned.

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See related article on pp 917-929.

* For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

SUMMARY OF THE RECOMMENDATION

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate-specific antigen (PSA) testing or digital rectal examination (DRE). This is a **grade I recommendation.** (See **Appendix** Table 1 for a description of the USPSTF classification of recommendations.)

The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. (See **Appendix** Table 2 for a description of the USPSTF classification of levels of evidence.) *Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cases of cancer that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.*

CLINICAL CONSIDERATIONS

Prostate-specific antigen testing and DRE can effectively detect prostate cancer in its early pathologic stages. Recent evidence suggests that radical prostatectomy can reduce prostate cancer mortality in men whose cancer is detected clinically. The balance of potential benefits (the reduction of morbidity and mortality from prostate cancer) and harms (false-positive results, unnecessary biopsies, and possible complications) of early treatment of the types of cancer found by screening, however, remains uncertain. Therefore, the benefits of screening for early prostate cancer remain unknown. Ongoing screening trials, and trials of treatment versus "watchful waiting" for cancer detected by screening, may help clarify the benefits of early detection of prostate cancer.

Despite the absence of firm evidence of effectiveness, some clinicians may opt to perform prostate cancer screening for other reasons. Given the uncertainties and controversy surrounding prostate cancer screening, clinicians should not order the PSA test without first discussing with the patient the potential but uncertain benefits and the possible harms of prostate cancer screening. Men should be informed of the gaps in the evidence, and they should be assisted in considering their personal preferences and risk profile before deciding whether to be tested.

If early detection improves health outcomes, the population most likely to benefit from screening will be men 50 to 70 years of age who are at average risk and men older than 45 years of age who are at increased risk (African-American men and those with a first-degree relative with prostate cancer) (1). Benefits may be smaller in Asian-American persons, Hispanic persons, and persons in other racial and ethnic groups that have a lower risk for prostate cancer. Older men and men with other significant medical problems who have a life expectancy of fewer than 10 years are unlikely to benefit from screening (1).

Prostate-specific antigen testing is more sensitive than DRE for the detection of prostate cancer. Prostate-specific antigen screening with the conventional cut-point of 4.0 ng/dL detects a large majority of prostate cancer; however, a significant percentage of early prostate cancer (10% to 20%) will be missed by PSA testing alone (2). Using a lower threshold to define an abnormal PSA level detects more cases of cancer at the cost of more false-positive results and more biopsies.

The yield of screening in terms of cancer detected declines rapidly with repeated annual testing (1). If screening were to reduce mortality, biennial PSA screening could yield as much benefit as annual screening.

The brief review of the evidence that is normally included in USPSTF recommendations is available in the complete recommendation and rationale statement on the USPSTF Web site (www.preventiveservices.ahrq.gov).

RECOMMENDATIONS OF OTHERS

Most major U.S. medical organizations recommend that clinicians discuss with patients the potential benefits and possible harms of PSA screening, consider patient preferences, and individualize the decision to screen. They generally agree that the most appropriate candidates for screening include men older than 50 years of age and younger men at increased risk for prostate cancer but that screening is unlikely to benefit men who have a life expectancy of fewer than 10 years. These organizations include the American Academy of Family Physicians, the American Cancer Society, the American College of Physicians–American Society of Internal Medicine, the American Medical Association, and the American Urological Association (3–7). None of these organizations endorses universal or mass screening for any group of men. In 1994, the Canadian Task Force on Preventive Health Care recommended against the routine use of PSA or transrectal ultrasonography as part of the periodic health examination (8); while recognizing the limitations of DRE, it concluded that the evidence was insufficient to recommend that physicians discontinue use of DRE in men 50 to 70 years of age. The Canadian Task Force is in the process of updating its recommendations.

APPENDIX

Members of the U.S. Preventive Services Task Force are Alfred O. Berg, MD, MPH, *Chair* (University of Washington, Seattle, Washington); Janet D. Allan, PhD, RN, *Vice-Chair* (Dean, School of Nursing, University of Maryland, Baltimore, Baltimore, Maryland); Paul Frame, MD (Tri-County Family Medicine, Cohocton, and University of Rochester, Rochester, New York); Charles J. Homer, MD, MPH (National Initiative for Children's Healthcare Quality, Boston, Massachusetts); Mark S. Johnson, MD, MPH (University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey); Jonathan D. Klein, MD, MPH (University of Rochester School of Medicine, Rochester, New York); Tracy A. Lieu, MD, MPH (Harvard Pilgrim Health Care and Harvard Medical School, Boston, Massachusetts); Cynthia D. Mulrow, MD, MSc (University of Texas Health Science Center, San Antonio, Texas [member and affiliation at time recommendation was finalized]); C. Tracy Orleans, PhD (The Robert Wood Johnson Foundation, Princeton, New Jersey); Jeffrey F. Peipert, MD, MPH (Women and Infants' Hospital, Providence, Rhode Island); Nola J. Pender, PhD, RN (University of Michigan, Ann Arbor, Michigan); Albert L. Siu, MD, MSPH (Mount Sinai School of Medicine, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Co., Inc., West Point, Pennsylvania); Carolyn Westhoff, MD, MSc (Columbia University, New York, New York); and Steven H. Woolf, MD, MPH (Virginia Commonwealth University, Fairfax, Virginia).

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

Appendix Table 1. **U.S. Preventive Services Task Force Grades and Recommendations***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

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Screening for Prostate Cancer: An Update of the Evidence for the U.S. Preventive Services Task Force

Russell Harris, MD, MPH, and Kathleen N. Lohr, PhD

Background: **In U.S. men, prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer death. Screening for prostate cancer is controversial.**

Purpose: **To examine for the U.S. Preventive Services Task Force the evidence of benefits and harms of screening and earlier treatment.**

Data Sources: **MEDLINE and the Cochrane Library, experts, and bibliographies of reviews.**

Study Selection: **Researchers developed eight questions representing a logical chain between screening and reduced mortality, along with eligibility criteria for admissible evidence for each question. Admissible evidence was obtained by searching the data sources.**

Data Extraction: **Two reviewers abstracted relevant information using standardized abstraction forms and graded article quality according to Task Force criteria.**

Data Synthesis: **No conclusive direct evidence shows that screening reduces prostate cancer mortality. Some screening tests can detect prostate cancer at an earlier stage than clinical detection. One study provides good evidence that radical prostatectomy reduces disease-specific mortality for men with localized prostate cancer detected clinically. No study has examined the additional benefit of earlier treatment after detection by screening. Men with a life expectancy of fewer than 10 years are unlikely to benefit from screening even under favorable assumptions. Each treatment is associated with several well-documented potential harms.**

Conclusions: **Although potential harms of screening for prostate cancer can be established, the presence or magnitude of potential benefits cannot. Therefore, the net benefit of screening cannot be determined.**

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For author affiliations, see end of text.

See related article on pp 915-916.

The American Cancer Society estimates that 189 000 men will receive a diagnosis of prostate cancer in 2002 and that 30 200 men will die of the disease (1). Many more men receive a diagnosis of prostate cancer than die of it (lifetime risk, about 1 in 6 vs. about 1 in 29). Among types of cancer, only lung cancer kills more men each year. The cause of prostate cancer is unknown, and the best-documented risk factors (age, ethnicity, and family history) are not modifiable. The burden of prostate cancer falls disproportionately on men who are older or black. The median age at diagnosis is approximately 71 years, and the median age at death is 78 years (2). More than 75% of all cases of prostate cancer are diagnosed in men older than 65 years of age, and 90% of deaths occur in this age group (2, 3). Incidence is approximately 60% higher and mortality rate is twofold higher in black men than in white men (2). Asian-American men and Hispanic men have lower incidence rates than non-Hispanic white persons (3).

Although approaches to primary prevention of prostate cancer are being tested, to date none are known to be effective. The most common strategy for reducing the burden of prostate cancer is screening, but screening remains controversial. Many studies on this topic have been published since 1996, when the U.S. Preventive Services Task Force (USPSTF) last examined prostate screening (4). To assist the USPSTF in updating its recommendation, the Research Triangle Institute–University of North Carolina Evidence-based Practice Center performed a systematic review of the evidence on screening for prostate cancer.

METHODS

Using USPSTF methods (5), we developed an analytic framework and eight key questions to guide our literature search. Because we found no direct evidence connecting screening and reduced mortality, we searched for indirect evidence on the yield of screening, the efficacy and harms of various forms of treatment for early prostate cancer, and the costs and cost-effectiveness of screening. We developed eligibility criteria for selecting relevant evidence to answer the key questions (**Table 1**). We examined the critical literature from the 1996 USPSTF review and used search terms consistent with the eligibility criteria to search the MEDLINE database and Cochrane Library for English-language reviews and relevant studies published between 1 January 1994 and 15 September 2002.

The first author and at least one trained assistant reviewed abstracts and articles to find those that met the eligibility criteria. For these studies, the two reviewers abstracted relevant information using standardized abstraction forms. We graded the quality of all included articles according to USPSTF criteria (5). The authors worked closely with two members of the USPSTF throughout the review and periodically presented reports to the full USPSTF. We distributed a draft of the systematic evidence review to experts in the field and relevant professional organizations and federal agencies for broad-based external peer review and made revisions based on the feedback. We then revised the full systematic evidence review into this manuscript. A more complete account of the methods of this review can be found in the Appendix (available at

Table 1. **Key Questions, Inclusion Criteria, and Articles Meeting Criteria***

Key Question	Inclusion Criteria	Articles Meeting Criteria, *n*
All	Published from 1 January 1994 to 15 September 2002 English language MEDLINE, Cochrane Human participants	
1. Efficacy of screening (direct evidence)	RCT; case–control study; or ecologic evidence directly connecting screening with health outcomes	1 RCT 2 case–control 15 ecologic
2. Yield of screening	Unselected population without prostate cancer Screening test offered to all Work-up offered to all with positive results on screening tests Screening test compared with a valid reference standard	35
3. Efficacy of radical prostatectomy	RCT; clinically localized disease Follow-up ≥2 years ≥75% of patients followed	1
4. Efficacy of radiation therapy	Health outcomes	0
5. Efficacy of androgen deprivation therapy		2
6. Efficacy of watchful waiting		1
7. Harms of treatment	Patient self-report Use of valid measurement instrument Follow-up from pretreatment to at least 12 months post-treatment *or* Comparison with similar untreated control group at least 12 months post-treatment	32
8. Costs and cost-effectiveness of treatment	Valid assessment of costs of screening and treatment Assess direct and indirect costs Cost-effectiveness, cost-benefit, cost-utility Modeling studies	2

* RCT = randomized, controlled trial.

www.annals.org). The complete systematic evidence review is available on the Web site of the Agency for Healthcare Research and Quality (www.ahrq.gov) (6).

This evidence report was funded through a contract to the Research Triangle Institute–University of North Carolina Evidence-based Practice Center from the Agency for Healthcare Research and Quality. Staff of the funding agency and members of the USPSTF contributed to the study design, reviewed draft and final manuscripts, and made editing suggestions.

RESULTS

Direct Evidence That Screening Reduces Mortality

Randomized, Controlled Trials

Labrie and colleagues (7) completed the first randomized, controlled trial (RCT) of prostate cancer screening with more than 46 000 men. At the end of 8 years of follow-up, approximately 23% of the invited group and 6.5% of the not-invited group had been screened with prostate-specific antigen (PSA) testing and digital rectal examination (DRE). Prostate cancer death rates did not differ between groups (4.6 vs. 4.8 deaths per 1000 persons, respectively).

Two other RCTs of prostate cancer screening, both initiated in 1994, are ongoing: the U.S. National Cancer Institute Prostate, Lung, Colorectal, and Ovary Trial and the European Randomized Study of Screening for Prostate Cancer. Neither study will have data on mortality for several more years.

Case–Control Studies

Three well-conducted, nested case–control studies (two since 1994) examined the relationship between chart review documentation of DRE and advanced prostate cancer or death from prostate cancer. Two studies found no relationship (8, 9). The third study found that men who died of prostate cancer had fewer DREs in the years before diagnosis (odds ratio indicating a protective effect of DRE, 0.51 [95% CI, 0.31 to 0.84]) (10).

Why results from these otherwise similar studies differ is not clear. The three studies depended on large databases and on individual medical records. They defined cases slightly differently and used different approaches to differentiate screening DRE from diagnostic DRE. Because such studies are complex in design, we were not able to determine whether one method was more accurate than another (11). All three studies were small, and all were consistent with a reduction in prostate cancer mortality of up to 50% with DRE.

We found no case–control studies of PSA screening. This can be explained, at least in part, by the fact that insufficient time has elapsed since the introduction of PSA as a screening test in the late 1980s. Such studies are under way (12).

Ecologic Studies

Around 1987, use of PSA screening began to increase rapidly in the United States. Important trends in prostate cancer incidence and mortality also occurred at that time. Although incidence rates had been slowly increasing for some years before 1987, data from the U.S. Surveillance, Epidemiology, and End Results program showed a dramatic increase in age-adjusted prostate cancer incidence—20% per year—from 1989 to 1992. The rates then decreased at 10.8% per year (13), stabilizing after 1994 (14). Most of the increase in incidence was seen in localized or regional disease. Incidence of distant-stage disease at diagnosis showed little initial increase and then began to decline; annual decline for white men was 17.9% after 1991 (15).

Disease-specific mortality rates paralleled trends in prostate cancer incidence (15, 16). In the late 1980s, the average annual percentage increase rose from 0.7% to 3.1% for white men and from 1.6% to 3.2% for black men. In 1991, prostate cancer mortality rates for white men began to decline (21.6% decrease from 1991 to 1999); in 1993, rates for black men followed suit (16.0% decrease from 1993 to 1999) (14). Mortality rates decreased in all age groups at about the same time. Analyses of trends in prostate cancer incidence and mortality in Olmsted County, Minnesota (17), and in Canada (18, 19) have shown similar results.

Ecologic evidence is difficult to interpret. Although screening probably explains trends in incidence of prostate cancer (20), trends in mortality are more difficult to understand. Some aspects of the trends (for example, a decline in distant-stage disease) are consistent with screening, but other aspects (for example, the short time between increased screening and decreased mortality) (21) are not as consistent with our current view of the natural history of prostate cancer. The argument that the decline in mortality can be attributed to PSA screening would be stronger if it could be shown that the decline was largest in areas with more screening. To date, data on this issue are conflicting (19, 22–27).

Other possible explanations for decreased mortality include "attribution bias" and improved treatment. Attribution bias suggests that some deaths are mistakenly attributed to prostate cancer. If the percentage of deaths so attributed is stable, then the prostate cancer mortality rate would be expected to increase and decrease in close approximation with the incidence of prostate cancer in the population (16).

Changes in prostate cancer treatment during the late 1980s and early 1990s included higher rates of radical prostatectomy, development of luteinizing hormone–releasing hormone (LHRH) agonists (allowing improved androgen deprivation therapy without castration), and refinements in radiation therapy. Such changes may explain the reduction in prostate cancer mortality. A recent study by Bartsch and coworkers (27), for example, documented a greater reduction in prostate cancer mortality in the Austrian state of Tyrol, which had instituted a free PSA screening program, compared with the rest of Austria. This finding could be a consequence of the screening program, changes in treatment that accompanied the screening program, misattribution of cause of death, or some combination of the three.

Accuracy of Screening

Three problems complicate any attempt to determine the accuracy of screening tests for prostate cancer. First, research has yet to clarify which tumors screening should target. Second, the reference standard (prostate biopsy) for diagnosing prostate cancer after positive results on a screening test is imperfect. Third, few studies perform biopsy on men with negative results on screening tests.

Prostate cancer is a heterogeneous tumor. Different cases of prostate cancer have widely varying growth rates and potential for causing death. Ideally, prostate cancer screening would target only tumors that would cause clinically important disease. Currently available prognostic markers can distinguish a small number of men with excellent prognosis for long-term survival and a small number of men with poor prognosis for long-term survival (28). However, they cannot help us correctly categorize the prognosis of those in the middle category, which includes most men with prostate cancer (29–33). Since research has not yet clearly defined the characteristics of clinically important prostate cancer, we do not know what the specific target of screening should be.

The usual reference standard used in prostate cancer screening studies, transrectal needle biopsy of the prostate, is imperfect for two reasons. First, it misses some cases of cancer; 10% to 30% of men who have negative results on an initial series of biopsies have cancer on repeated biopsy series (34–39). Thus, some men categorized as not having cancer actually have it, falsely lowering the test's measured sensitivity. Second, in clinical practice and research, a "biopsy" is actually four to six (or more) biopsies. Many biopsy specimens are obtained, most from normal-appearing areas of the prostate. An analysis of this practice concluded that up to 25% of apparently PSA-detected tumors and more than 25% of apparently DRE-detected tumors were likely to have been detected by serendipity, that is, as an incidental finding on a blind biopsy (40). Thus, some men who are categorized as having cancer detected by screening actually have serendipity-detected cancer. This error falsely increases sensitivity.

In addition to problems of the accuracy of the reference standard, few studies perform biopsy on men who have negative results on screening tests. This reduces our ability to determine the number of false-negative screening tests and to calculate sensitivity. Most studies use several noninvasive tests together, measuring the sensitivity of one test against the combined findings of all tests. The extent to which these combined tests actually detect all important cancer is unknown. This bias probably leads to an overestimate of sensitivity.

Screening Methods

Prostate-Specific Antigen Testing

An analysis from the Physicians' Health Study avoided some of the bias of the problematic reference standard by using longitudinal follow-up instead of biopsy (41). In this study, which used a PSA cut-point of 4.0 ng/mL or higher, the sensitivity for detecting cancer appearing within 2 years after screening was 73.2%. Although the study calculated sensitivity separately for aggressive (that is, extracapsular or higher grade) and nonaggressive (that is, intracapsular and lower grade) cancer (sensitivity, 91% vs. 56%), it is not clear that these categories correspond to clinically important and clinically unimportant tumors. Among men who did not receive a diagnosis of prostate cancer in those 2 years, 14.6% had an initial PSA level of 4.0 ng/mL or greater, corresponding to a specificity of 85.4%.

Other studies have provided similar estimates of sensitivity and specificity for PSA level with a cut-point of 4.0 ng/mL (42–44). Specificity for PSA screening is lower among men with larger prostate glands, including the large number of older men with benign prostatic hyperplasia. One study of four carefully chosen samples found that the likelihood ratios for various PSA levels were much lower among men with benign prostatic hyperplasia than among men without benign prostatic hyperplasia (45). Thus, the PSA test is not as accurate in detecting cancer in men with benign prostatic hyperplasia as in those without.

Because of the reduced specificity in older men with benign prostatic hyperplasia, some experts have proposed that the PSA cut-point be adjusted for age, with higher cut-points for older men and lower cut-points for younger men (46). Such a strategy increases sensitivity and lowers specificity in younger men, while the reverse is true in older men. Experts disagree about whether this strategy would improve health outcomes (47, 48).

Some experts have also proposed decreasing the cut-point defining an abnormal PSA level from 4.0 ng/mL to 3.0 ng/mL (or even 2.6 ng/mL) for all men (44, 49, 50). This approach results in more biopsies and more cancer detected (49, 51–55). Because of the uncertainty about the definition of clinical importance, the value of this increased detection is unknown.

In the serum, PSA circulates in two forms: free and complexed with such molecules as α_1-antichymotrypsin. Men with prostate cancer tend to have a lower percentage of free PSA than men without prostate cancer (56, 57). In research, the percentage of free PSA (or a similar test measuring the level of complexed PSA) (58–62) has mainly been used to increase the specificity of screening by distinguishing between men with PSA levels of 4.0 ng/mL to 9.9 ng/mL who should undergo biopsy and those who should not (52, 63–70). Different studies have suggested different cut-points for percentage of free PSA; a lower cut-point avoids more biopsies but also misses more cancer. High cut-points (for example, 25%) would avoid about 20% of biopsies, and the probability of cancer at that cut-point is about 8% (66). In practice, it is not clear whether this probability would be low enough for men and their physicians to forgo biopsy (71).

Men with prostate cancer have a greater increase in PSA level over time than men without cancer (72). It is unclear, however, whether examining the annual rate of change in PSA level (PSA velocity) improves health outcomes or reduces unnecessary biopsies (47, 73). Because of intraindividual variation, PSA velocity is useful only in men who have three or more tests of PSA level over a period of 1 to 3 years (47, 74, 75).

Digital Rectal Examination

It is more difficult to detect cancer with DRE than with PSA. A meta-analysis examining studies of DRE in unselected samples screened by both PSA and DRE found a sensitivity of 59% (64% for the four best studies) (76). Digital rectal examination detects cancer in some men with PSA levels below 4.0 ng/mL (positive predictive value, about 10% according to one large study [63]) or even 3.0 ng/mL, but the tumors were usually small and well differentiated (77). Digital rectal examination has limited reproducibility (78).

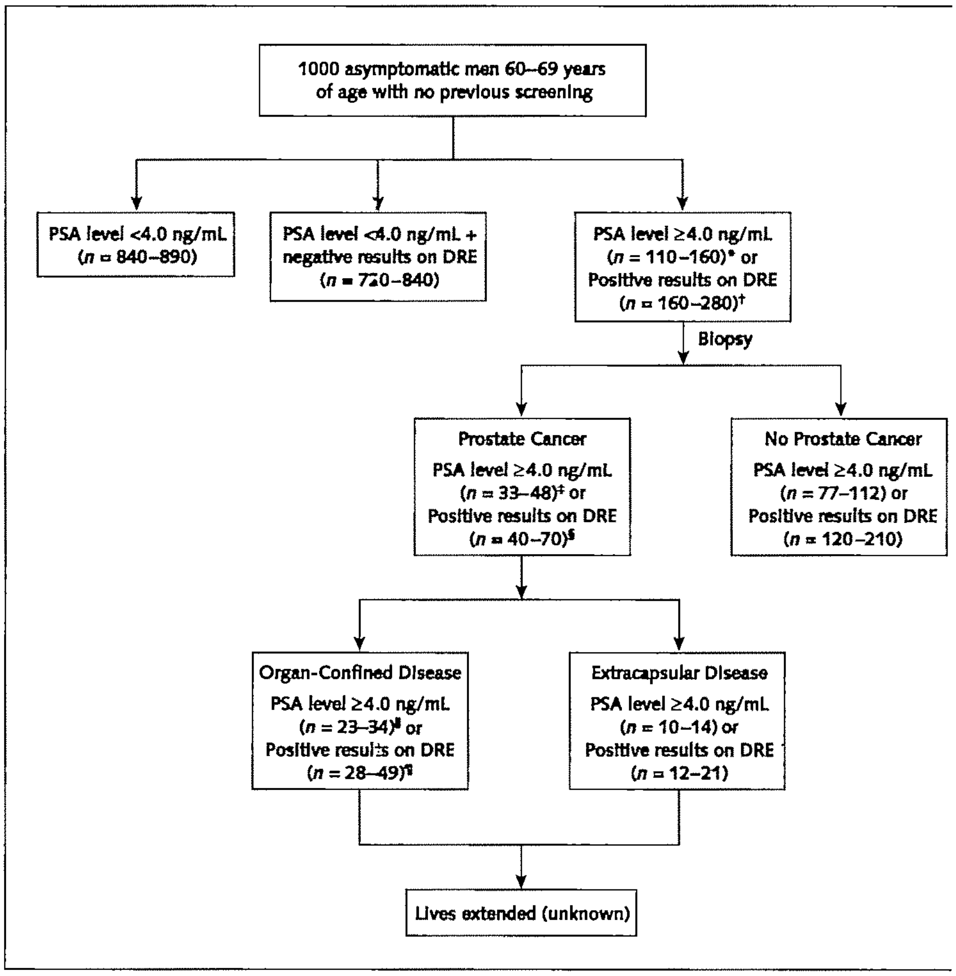
Yield of Large Screening Programs

Using six studies of screening with a single PSA test or with PSA and DRE among large, previously unscreened samples, we were able to estimate the yield of a new screening program among men in different age groups (79) who had not previously been screened (7, 44, 49, 63, 64, 79–83). The **Figure** gives estimates of positive test results and cases of cancer detected after screening with PSA alone or screening with PSA and DRE among men in their 60s. Men in their 50s have fewer positive test results and cases of cancer detected, while men in their 70s have more.

The percentage of participants with a PSA level of 4.0 ng/mL or higher ranged from about 4% (79) among men in their 50s to about 27% (64) among men in their 70s. The percentage of men who had a PSA level of 4.0 ng/mL or higher or abnormal results on DRE ranged from 15% among younger men to 40% among older men (79). Few other screening tests have such a high percentage of positive results (63, 64, 81, 82).

In the screening studies, some men with abnormal results on screening tests did not undergo biopsy. If we assume that biopsy is performed on all men with an abnor-

Figure. **Estimated yield of screening with prostate-specific antigen (*PSA*) testing or with PSA testing and digital rectal examination (*DRE*).**


1000 asymptomatic men 60–69 years of age with no previous screening
PSA level <4.0 ng/mL (n = 840–890)
PSA level <4.0 ng/mL + negative results on DRE (n = 720–840)
PSA level ≥4.0 ng/mL (n = 110–160)* or Positive results on DRE (n = 160–280)†
Biopsy
Prostate Cancer PSA level ≥4.0 ng/mL (n = 33–48)‡ or Positive results on DRE (n = 40–70)§
No Prostate Cancer PSA level ≥4.0 ng/mL (n = 77–112) or Positive results on DRE (n = 120–210)
Organ-Confined Disease PSA level ≥4.0 ng/mL (n = 23–34)|| or Positive results on DRE (n = 28–49)¶
Extracapsular Disease PSA level ≥4.0 ng/mL (n = 10–14) or Positive results on DRE (n = 12–21)
Lives extended (unknown)

The number of cancer cases detected would be smaller after repeated annual screening. * For men in their 50s, $n = 50$; for men in their 70s, $n = 270$. † For men in their 50s, $n = 150$; for men in their 70s, $n = 400$. ‡ For men in their 50s, $n = 17$; for men in their 70s, $n = 90$. § For men in their 50s, $n = 30$; for men in their 70s, $n = 100$. ||For men in their 50s, $n = 12$; for men in their 70s, $n = 63$. ¶ For men in their 50s, $n = 21$; for men in their 70s, $n = 70$. In all footnotes, numbers are approximate.

mal result on a screening test and that the rate of cancer detection is the same as for men who undergo study biopsy, we estimate that the percentage of all men screened who would have prostate cancer detected would range from approximately 1.5% (PSA screening alone for men in their 50s) (81) to 10% (PSA and DRE screening for men in their 70s) (44).

The **Figure** gives general percentages from all studies. In these six studies, biopsies detected cancer in approximately 30% of men with a PSA level of 4.0 ng/mL or higher and in 20% to 27% of men with a PSA level of 4.0 ng/mL or higher or an abnormal result on DRE (7, 49, 79, 80, 83). The probability of prostate cancer with a PSA level of 2.5 ng/mL to 4.0 ng/mL and negative results on DRE is also about 20% (51). Although the studies found that 60% to 70% of screen-detected cancer is organ confined (7, 49, 80, 82, 83), they do not provide information about the number of lives extended by detecting either organ-confined or extracapsular tumors.

Yield with Different Screening Intervals

Rates of positive results and cancer detection decrease on screening a year after the initial screening round (7, 49, 80, 83–85). In one study, approximately 26% of men with a PSA level of 4.0 ng/mL or greater had prostate cancer after the first round of screening and approximately 6.2% had cancer after subsequent rounds (7). Other studies have concluded that annual screening confers little gain compared with intervals of at least 2 years (86), especially for the 70% of the population with PSA levels of 2.0 ng/mL or less (41, 87).

Effectiveness of Current Treatments for Localized Disease

Radical Prostatectomy

Since 1991, radical prostatectomy has been the most common treatment for clinically localized prostate cancer. It is the initial treatment for more than one third of patients with new diagnoses, most commonly men 75 years of age or younger (2). The procedure is usually performed with curative intent in men who have a life expectancy of at least 10 years.

One well-conducted RCT compared radical prostatectomy with "watchful waiting" (in which treatment is not given initially but is reserved for progressive or symptomatic disease) among men with clinically detected prostate cancer (88). About 75% of the men in this study had palpable cancerous tumors, few of which were the size usually detected by PSA screening (73, 84, 89). After 8 years of follow-up, 7.1% of the radical prostatectomy group had died of prostate cancer compared with 13.6% of men in the watchful waiting group (relative hazard, 0.50 [CI, 0.27 to 0.91]). The absolute difference in prostate cancer mortality was 6.6% (CI, 2.1% to 11.1%) (number needed to treat for benefit, 17). The groups did not differ in all-cause mortality.

No other well-conducted RCT has compared any other treatment with radical prostatectomy for clinically localized prostate cancer. One ongoing RCT, the Prostatectomy Intervention versus Observation Trial in the United States, will publish results in the future (90, 91).

One observational study that used internal controls and data from the Surveillance, Epidemiology, and End Results program provided information on the effectiveness of radical prostatectomy relative to other treatments (92). For men with well-differentiated cancer, 10-year disease-specific survival did not differ between the radical prostatectomy group and the age-matched radiation or watchful waiting groups. Disease-specific survival was slightly higher for the radical prostatectomy group in men with moderately differentiated tumors (radical prostatectomy group, 87%; radiation group, 76%; watchful waiting group, 77%) and was much higher for men with poorly differentiated cancer (radical prostatectomy group, 67%; radiation group, 53%; watchful waiting group, 45%). Other cohort studies without controls have found similar survival rates after radical prostatectomy (33, 93–97).

Radiation Therapy

Radiation therapy is the second most commonly used treatment for nonmetastatic prostate cancer and is the most common treatment for men 70 to 80 years of age (2). The two common types of radiation therapy reviewed here are external-beam radiation therapy (EBRT) and brachytherapy, the insertion of radioactive pellets directly into prostate tissue.

No well-conducted RCT with clinical outcomes compares EBRT with any other therapy for clinically localized prostate cancer. In the large cohort study discussed earlier (92), 10-year disease-specific survival rates in the EBRT group were similar to those in the watchful waiting group for men with well-differentiated and moderately differentiated tumors but were higher for men with poorly differentiated cancer (92).

Brachytherapy is most often used alone for men with well or moderately differentiated intracapsular prostate cancer or in combination with EBRT for men with more aggressive cancer. No RCT with clinical outcomes compared brachytherapy with any other treatment for prostate cancer. Two observational studies involving 100 or more patients with clinically localized prostate cancer found high survival rates for patients treated with radioactive gold or iodine seeds (98, 99).

Androgen Deprivation Therapy

The traditional approach to androgen deprivation therapy has been surgical bilateral orchiectomy. A newer approach uses LHRH agonists (for example, goserelin or leuprolide), a group of drugs that stimulate the release of luteinizing hormone from the pituitary gland. Paradoxically, when used clinically, LHRH agonists result in downregulation of pituitary receptors, thus markedly reducing the level of testosterone production to that of a castrated man. Luteinizing hormone–releasing hormone agonists have been used clinically since the late 1980s.

Two well-conducted RCTs compared clinical outcomes between men with clinically localized prostate cancer who were treated with androgen deprivation therapy (with orchiectomy [100] or estramustine [101]) and men treated with EBRT. Androgen deprivation therapy either increased overall survival (100) or reduced clinical recurrence (101); outcomes improved primarily among men who had lymph node involvement.

Four additional RCTs of androgen deprivation therapy (with LHRH agonists) as an adjuvant to EBRT or radical prostatectomy for locally advanced prostate cancer found statistically significant improved overall survival (10% to 20% absolute difference) in men who received androgen deprivation therapy (102–108). Another RCT of immediate versus deferred androgen deprivation therapy (with orchiectomy or LHRH agonists) and no other treatment found improved survival (8% absolute difference) for the immediate therapy group in men who had a new diagnosis of locally advanced prostate cancer (109).

Watchful Waiting

The term *watchful waiting* implies that no treatment is given initially but that the patient is followed for evidence of progressive or symptomatic disease, for which treatment might be offered. Because the only well-conducted RCT that compares watchful waiting and more aggressive treatment examined men with prostate cancer detected clinically rather than by screening (88), the best information about the outcomes of watchful waiting comes from observational studies of men who, for various reasons, were not treated for prostate cancer. These studies also provide information about the natural history of the disease.

Four well-conducted retrospective cohort studies (29, 30, 110, 111) and one pooled analysis of six other cohort studies (28) provide information about survival with untreated prostate cancer. Men with well-differentiated, clin-

Table 2. **Harms of Treatment***

Treatment	Men with Reduced Sexual Function	Men with Urinary Problems	Men with Bowel Problems	Men with Other Symptoms
	←	%		→
Radical prostatectomy	20–70	15–50		
External-beam radiation therapy	20–45	2–16	6–25	
Brachytherapy	36†	6–12†	18†	
Androgen deprivation therapy (LHRH agonists)	40–70			Breast swelling: 5–25 Hot flashes: 50–60

* Values are percentages of men treated who had side effects at least 12 months after treatment. LHRH = luteinizing hormone–releasing hormone.
† These findings are less certain than other entries because they are based on less or inferior evidence.

ically localized prostate cancer have excellent long-term survival, with little or no reduction in survival compared with similar men without prostate cancer. Men with poorly differentiated cancer have reduced survival. In one study, 10-year survival was 17% in men with poorly differentiated cancer and 47% in age-matched controls without prostate cancer (92).

Because most prostate cancer detected today by screening is moderately differentiated, survival of men with this type of tumor is important to the debate about screening. On the standard histologic grading system for prostate cancer, these men have tumors with Gleason scores of 5 to 7. Gleason scores range from 2 to 10; lower scores indicate well-differentiated patterns, and higher scores indicate more poorly differentiated tumors.

The most detailed analysis of men with untreated, clinically localized, moderately differentiated cancer found that 15-year prostate cancer–specific survival rates ranged from 30% (Gleason score of 7 in men 50 to 59 years of age) to 94% (Gleason score of 5 in men 50 to 59 years of age) (29, 110). Men in their 70s had survival rates similar to those of men in their 50s for tumors with a Gleason score of 5 but much better survival for tumors with a Gleason score of 7 (58% vs. 30%). Because men in this study received their diagnoses in the pre-PSA era, survival would probably be even better in similar men receiving diagnoses today given the "lead time" added by earlier detection.

Harms of Treatment

Because harms of treatment are experienced by the men themselves, and because men may have problems that are similar to treatment harms but are not attributable to treatment, we prioritized evidence that measured patients' perceptions of their own function. For comparison, we used an untreated group or the same men examined before and at least 12 months after treatment.

Radical Prostatectomy

Thirty-day mortality rates after radical prostatectomy range from 0.3% to 1% for most men and may be higher for men older than 80 years of age (112–116). The primary long-term adverse effects of radical prostatectomy include erectile dysfunction and urinary incontinence (**Table 2**). At least 20%, perhaps as many as 70%, of men have worsened sexual function as a result of radical prostatectomy (114, 117–135). Fifteen percent to 50% of men who had a radical prostatectomy had some urinary problems 1 year later (112, 114, 117, 119, 121, 123, 126, 127, 131, 132, 135–138). Current evidence is mixed about the extent to which, outside of excellent academic centers (95, 124), the newer nerve-sparing procedure reduces complication rates.

Radiation Therapy

Twenty percent to 45% of men with no erectile dysfunction and 2% to 16% of men with no urinary incontinence before EBRT developed dysfunction 12 to 24 months afterward (**Table 2**) (117, 123, 126–131, 135, 137, 139–146). Six percent to 25% of men who had no bowel dysfunction before EBRT reported marked problems 12 or more months afterward (117, 123, 125, 126, 130, 131, 135, 137, 140, 142, 144–147). The evidence is mixed about whether newer techniques, including three-dimensional conformal EBRT, reduce the frequency of urinary or bowel side effects.

Compared with EBRT or radical prostatectomy, fewer high-quality studies of the harms of brachytherapy have been completed. Our estimates are therefore less precise for this treatment. Among men who were potent before treatment, about 21% are impotent and 36% have decreased erectile function 3 years after brachytherapy (148, 149). A majority of men will have distressing urinary symptoms in the first months after brachytherapy, and 6% to 12% will have such symptoms 1 year later. Up to 25% of men will have some lack of urinary control 12 months after brachytherapy (120, 149–151). Approximately 18% of men will have diarrhea 1 year later (120), and 19% will have some persistent rectal bleeding 12 to 28 months later (152).

Androgen Deprivation Therapy

We focused on the harms of LHRH agonists because the effectiveness studies we reviewed primarily used this type of androgen deprivation therapy. No study has examined reports from the same patients beginning before androgen deprivation therapy and extending for at least 1 year. Our best information comes from two large national studies (153–155) and a systematic review (156, 157). Compared with untreated men, 40% to 70% of men who were sexually active before treatment were not sexually active afterward (**Table 2**). Five percent to 25% of men had breast swelling, and 50% to 60% had hot flashes. Mean scores on quality-of-life indices are lower for men treated with androgen deprivation therapy (154). One RCT of LHRH adjuvant therapy found similar results (107). Potential long-term complications of LHRH therapy include lack of vitality, anemia, and osteoporosis (155, 158, 159). The frequency and severity of these complications are not yet clear.

Quality of Life

Litwin and colleagues (129) compared overall quality-of-life scores among controls and men with prostate cancer within treatment groups. Although they found the same differences in specific symptoms as noted earlier, they found no differences among groups (either among treatment groups or between men with and without prostate cancer) in overall quality of life.

Cost-Effectiveness of Screening

Given the uncertainties about the existence and magnitude of benefits, the cost-effectiveness of screening for prostate cancer has been difficult to calculate. A 1993 decision analysis, which made optimistic assumptions about benefit from screening and early treatment, found little or no benefit for men with well-differentiated tumors (160). For men with moderately or poorly differentiated cancer, screening and early treatment could offer as much as 3.5 years of improvement in quality-adjusted life expectancy, again using the most optimistic assumptions. Even with optimistic assumptions, however, men 75 years of age and older were not likely to benefit from screening and aggressive treatment. One major reason is that any benefits of screening are expected to accrue some years in the future, after many men in this age group have died of some other condition. Two subsequent decision analyses have reached the same conclusions (161, 162).

In 1995, Barry and coworkers (163) published a cost-effectiveness analysis using favorable screening assumptions. The marginal cost-effectiveness of screening men 65 years of age with PSA and DRE, without adjustment for quality of life and without discounting benefits, was between $12 500 and $15 000 per life-year saved. Changing only a few assumptions, however, quickly increased the marginal cost-effectiveness ratio to above $100 000 per life-year saved. This ratio would be even less favorable if a decrement in quality of life associated with the harms of treatment were considered. In 1997, these investigators updated their model with newer data and further assumptions favorable to screening; findings were similar (164).

DISCUSSION

Prostate-specific antigen testing and, to a lesser extent, DRE can detect prostate cancer at an earlier stage than it could be detected clinically. A major problem in considering the utility of screening, however, is the heterogeneity of prostate cancer itself. The large discrepancy between prostate cancer diagnoses and deaths indicates that some and probably most tumors detected by screening are clinically unimportant. Because precise evidence regarding the prognosis of prostate cancer of various types is lacking, researchers have not been able to define the most appropriate targets of screening, that is, the types of cancer that will cause clinical symptoms and death and that can be treated better if detected earlier.

The efficacy of various types of treatment for clinically localized prostate cancer, and especially for the types of localized prostate cancer detected by screening, is largely unknown. Although one RCT found that radical prostatectomy reduced prostate cancer mortality compared with watchful waiting among men with symptomatic localized cancer, the magnitude of any additional benefit of detection and earlier treatment due to screening is still unknown. We lack direct evidence that EBRT, brachytherapy, or androgen deprivation therapy is effective for clinically localized cancer. Each treatment for prostate cancer is associated with various potential harms, including sexual, urinary, and bowel dysfunction.

The costs of a screening program for prostate cancer are potentially high. If treatment is extremely efficacious, then the cost-effectiveness of screening men 50 to 69 years of age may be reasonable; if treatment is less efficacious, the results may be net harm and high costs. Assuming that any potential benefit to screening accrues only after some years, men with a life expectancy of fewer than 10 years are unlikely to benefit. Because prostate cancer incidence and mortality rates are higher among black men, beneficial screening could have a larger absolute benefit in this ethnic group than in white men. The same uncertainties about screening, however, would apply.

Two RCTs of screening are in progress. Because of the problem of screening in control groups, however, some experts fear that even these trials may not provide a definitive answer about screening efficacy. If these trials find a reduction in prostate cancer mortality, further research will be required to determine whether the benefits outweigh the harms and costs for individuals or as a general policy. Research can help by developing new screening and treatment approaches that minimize harms and costs. If the trials show no benefit, research on other approaches to disease control, such as chemoprevention, will be necessary. In the interim, the efficacy of screening for prostate cancer remains uncertain.

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EDITORIAL

The Who, What, When, Where, Whom, and How of Hospitalist Care

Desires to improve inpatient care fueled the development of the hospitalist movement. To advocates of the movement, it seemed obvious that physicians who focused on hospital care would achieve better outcomes than physicians who spent most of their time in outpatient settings (1). Others, however, argued that hospitalists disrupted the continuum of care and would adversely affect clinical outcomes and patient satisfaction (2–4). Only research could resolve these disputes, and at least 19 observational studies have evaluated hospitalists' care (5). The studies, conducted mostly in academic settings with historical controls, small numbers of hospitalists, and selected patients, have generally found that hospitalist care was associated with important reductions in average length of stay and costs. Few studies tested for associations between hospitalists and clinical outcomes, and, among these studies, few found consistent relationships.

In this issue, two studies by Auerbach (6) and Meltzer (7) and colleagues corroborate past research and are the first to report that hospitalists' outcomes, including patient survival, improve as hospitalists gain experience. Given these results, is it time to recommend that hospitalists care for all hospitalized patients? In considering such a recommendation, we ask two difficult questions. First, does research show that important outcomes are substantively different and better in systems where hospitalists provide care? Second, if there are differences, are they due to the hospitalists or to something else?

The answer to the first question depends on the relative value that we place on patient-centered outcomes (symptoms, function, time to recovery, and mortality), physician-centered outcomes (career satisfaction, retention, pay), patient–physician relationships (satisfaction, trust), and system-centered outcomes (consultation rates, continuity of care, costs). In our opinion, Auerbach and Meltzer and colleagues provide the current best evidence about many outcomes. They used concurrent controls, tried to adjust for differences in case mix, and examined temporal changes. Both studies found that hospitalists' care was associated with changes in some important outcomes (length of hospital stay, mortality, and costs) but not others (readmission rates, consultation rates, self-reported health status, and emergency department visits). Neither reported any significant adverse outcomes of hospitalists' care, and neither examined physician outcomes or patient–physician relationships. Decreased length of stay and hospital costs were most apparent in the second year of both studies, suggesting that some of the benefits of hospitalist care surface as hospitalists gain experience. We think these studies show that outcomes can be better when hospitalists provide care.

That said, however, readers should interpret the mortality findings cautiously. Meltzer and colleagues found that the proportion of patients who died within 30, 60, or 365 days was generally similar for hospitalists and nonhospitalists, except for differences of borderline statistical significance in year 2. Larger studies with similar or larger effects would increase our confidence that the reported benefit is real. The study by Auerbach and colleagues reported reduced mortality for hospitalists' patients in both years of the study. In the Auerbach study, hospitalists' patients differed substantially from nonhospitalists' patients, raising concern about the extent to which their statistical analyses could adjust for potential confounding factors that influence mortality. We would have more confidence in the differences in mortality if both studies had provided information about how hospitalists' decisions and actions could have affected mortality. Confirming the mortality findings and exploring their mechanisms should be a priority for future investigations.

To answer the second question—are the observed differences due to hospitalists or to something else?—we tried to disentangle the various components of the complex intervention called "hospitalists" by asking, "Who delivers what to whom when, where, and how?"

Who? Hospitalists, who are experts in the clinical and logistic aspects of complex hospital care, are available to inpatients, families, and consultants throughout the day. Each hospitalist in Auerbach and colleagues' study cared for an average of 324 inpatients per year compared with 29 for each community physician. If rapid response matters and practice makes perfect, hospitalists should be effective. Yet Auerbach studied only five hospitalists and Meltzer studied only two, too few to determine whether the results were due to these particular physicians or to the fact that they functioned as hospitalists.

What? Physicians use various strategies for dealing with problems, and common sense suggests that repetition ingrains and refines approaches. However, neither study provided insight into the approaches that distinguished hospitalist and nonhospitalist care.

To whom? Hospital outcomes depend greatly on the baseline health of patients. Hospitalist and nonhospitalist patients differed markedly in the Auerbach study. Neither study provided data on the social situations of study patients, which can also influence outcomes.

When? Hospitalists, because they are on site throughout the day, might attend to daily hospital tasks (for example, discharge) more promptly than nonhospitalists and might intervene earlier in times of crisis. Neither study examines issues related to the timing of care.

Where? Hospitalists might have different effects depending on whether the hospital in which they work is large or small, private or public, with or without specialized units, or teaching or nonteaching. Meltzer and colleagues' study took place in an academic setting and Auerbach and colleagues' in a community setting, yet they had similar results.

How? The "how" is related to the mechanisms through which hospitalists' interventions work or do not work. These mechanisms include interactions with patients and other medical staff; diagnostic and management processes; and admission, discharge, and follow-up procedures. Resident physicians were an integral part of care for all patients in both studies, but neither study tells us much about how attending physicians and housestaff interacted.

While these two studies suggest that hospitalists can be associated with favorable outcomes, neither fully answers the question, "Who delivers what to whom when, where, and how?" We are therefore not certain that hospitalists caused the favorable outcomes. Conversely, neither study uncovered any evidence that hospitalists adversely influence hospital care.

The "who, what, where, when, whom, and how" question was a useful framework for our analysis of the effects of hospitalists, but it is a limited tool. The question itself starkly illustrates the problem: Physicians are but one component of a complicated system. Other aspects of care may influence outcomes more than physicians, and the interactions among all of these factors probably determine the success of systems of care. Fragmenting intricate interventions into component parts is a useful tool for first-order analysis of what actually happens in a complex system, but relying on it runs the risk of missing the ways in which the whole is greater than the sum of its parts.

The studies by Auerbach and Meltzer and colleagues and our common sense tell us that hospitalists can be an important advantage for improved systems of care. However, neither study proves that optimum hospital care requires hospitalists or tells us how hospitalists achieved favorable outcomes. Since hospitalists appear to be here to stay (8–10), it is critical that we understand how they achieve successful outcomes. We encourage researchers to study hospitalists' practices to identify optimal processes of care and the mixes of human and technical resources that fuel those processes. This research should explore the feasibility of interventions, identify patients most likely to benefit from hospitalist care, assess a panoply of outcomes, and measure patient and provider preferences. Investigators must be attentive to the costs and outcomes of care across the continuum from outpatient to inpatient to outpatient settings. We anticipate that many good descriptive studies, as well as an ongoing six-center, quasi-randomized 2-year trial funded by the Agency for Healthcare Research and Quality, will help us sort through these very timely and critical issues.

The Editors

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LETTERS

COMMENTS AND RESPONSES

Truth Survival

TO THE EDITOR: While we applaud Poynard and colleagues for addressing the issue of truth survival in clinical research (1), we feel that the data they collected are biased and misleading. Poynard and colleagues sampled studies on cirrhosis and hepatitis from 1945 to 1999. Experts were asked if the main conclusion from each study was true, false, or obsolete as of the year 2000. False or obsolete studies were considered to have the event of interest, and studies considered still true were censored at the year 2000. With this approach, the time to event should have been the time from publication of a research study until its results became either false or obsolete. For example, studies published in 1950 and made obsolete in 1965 would have 15 years of survival. However, Poynard and colleagues determined that truth survival was the time from publication to the year 2000. Therefore, a study published in 1950 and made obsolete in 1965 would be credited with 50 years of survival rather than the correct 15 years. This systematically overestimates the truth survival of false or obsolete research.

Even more problematic is that the overestimation selectively favors research with earlier publication dates, greatly inflating the truth survival of early research. Since the early research in Poynard and colleagues' sample was predominately nonrandomized, and no meta-analyses were found before 1980, it was predetermined that nonrandomized studies would appear to have greater 20-year truth survival than randomized trials or meta-analyses (87%, 85%, and 57%, respectively). Given Dr. Poynard's interest in evidence-based medicine (2), we doubt that this bias against meta-analyses and randomized trials was intentional. Indeed, Poynard and colleagues make it clear that their results were contrary to expectations. However, their data do not provide a sound basis for making this comparison.

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IN RESPONSE: We agree that very old publications declared obsolete or false in the year 2000 could cause the duration of survival to be overestimated if they were in fact obsolete or false many years earlier. However, this risk for survival overestimation does not concern the true conclusions that represent 60% of events.

For each obsolete or false conclusion, we estimated the year in which it became obsolete or false. Most often it was 1980 for biochemical liver tests; 1980 for corticosteroid treatment of hepatitis; and 1990 for non-A, non-B hepatitis, γ-globulin studies, and studies of portal hypertension. A new survival analysis was performed by using this new estimate of survival duration. With this new estimate, there was a small decrease of truth survival at 50 years for the mean percentage (±SE) of studies without false or obsolete conclusions (22% ± 4% vs. 26% ± 4% with the fixed estimate) but no difference in the percentage of studies without false conclusions (52% ± 5% vs. 53% ± 5% with the fixed estimate). The conclusions and the factors associated or not associated with truth survival did not change.

The 20-year mean survival (±SE) of studies without false or obsolete conclusions was lower in meta-analyses than in other studies (57% ± 10% vs. 73% ± 3%, respectively; log-rank = 11.3 [P = 0.008]); with the fixed estimate, these figures were 57% versus 87%. At 50 years, the survival was higher for negative than for positive conclusions (59% ± 10% vs. 15% ± 3%, respectively; log-rank = 19.4 [$P < 0.001$]). In randomized trials, the survival rate was higher for negative than for positive conclusions (76% ± 7% vs. 4% ± 4%, respectively, log-rank = 19.4 [$P < 0.001$]). Still, there was no significant difference between high (56% ± 10%) and low (21% ± 4%) methodologic quality (log-rank test = 0.32; $P > 0.2$).

The history of interferon in the treatment of hepatitis B remains the best example of the hazards of evidence-based medicine in hepatology. In 1980, clinicians perceived a negative conclusion from a single randomized trial as a major evidence-based result. We still need to be critical about our evidence-based "certainties."

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Ethics and the Medical Record

TO THE EDITOR: We wholeheartedly support Dr. Tauber's concern for improving patient care and the physician–patient relationship (1). However, we believe his proposal for a separate section in the medical record for ethical issues is problematic. Our chief objection is that virtually every aspect of clinical medicine is replete with ethical implications. Relegating selected ethical issues to a separate section in the medical record could easily encourage a minimalist view of ethics. Rather than trying to increase ethical sensitivity through requiring separate documentation, we believe this goal can be attained only by making systemic changes in medical education and by rewarding ethical awareness in clinical practice. Possible steps include 1) improving support for teaching behavioral sciences and ethics in the undergraduate medical curriculum and residency training, emphasizing the integration of these concepts throughout clinical practice; 2) increasing attention to the psychosocial aspects of the patient's life in the medical history so that understanding of the patient's life and illness in the context of family, community, and employment will be integrated into the body of the physician's notes; 3) mentoring junior physicians, modeling the values of compassion, respect for patients, and ethical sensitivity; 4) encouraging and rewarding ethical practices among attending physicians, residents, students, and administrators; and 5) developing relevant and valid instruments to evaluate skills in medical ethics.

Although a separate section in the medical record for ethics is well intended, the goal of cultivating ethical awareness and sensitivity to patients as persons will require a comprehensive approach involving incentives and reinforcement at all levels of medical training and practice.

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TO THE EDITOR: Dr. Tauber (1) addresses the phenomenon of a generation of physicians well equipped with technology but poorly adapted to manage the critical bioethical issues involving that very same technology. The partial solution he proposes is to include a section titled "Ethical Concerns" within the medical records. This could stir up a bit of controversy, especially if the physician documenting ethical concerns abides by the Hippocratic Oath. What, after all, does our medical oath say? The original Hippocratic Oath, the same one I took upon graduating from the University of California, Los Angeles, School of Medicine in 1984, states, "I will not give to a woman an instrument to produce abortion. With purity and holiness I will pass my life and practice my art." These indisputable words go beyond medicine and impact the very core of society (2, 3). Indeed, the expert medical witness at the Nuremberg medical trials (A.C. Ivy, MD) declared in 1949 that these trials truly brought to light the value and importance of the Hippocratic Oath (4).

It is startling, however, that Dr. Tauber suggests that the "dramatic settings of transplantation, in vitro fertilization, and abortion" not be included "because the ethical concerns of such decision making are integral to these clinical encounters." This loses the forest for the trees. Shall we go to a concentration camp and document in a chart an ethical concern of, say, proper emotional support for the guards while ignoring the real ethical atrocity at hand? That such a seeming contrast be called a "dramatic setting" is an understatement. Spectacularly nonsensical seems more apt.

It's like the popular majority in the fable "The Emperor's New Clothes" contrasted with the child who simply states the obvious, that is, that the emperor is naked. One would be hard pressed to think of anything more glaringly naked or in such direct violation of our medical Oath than the not-unprofitable extermination of innocent human life under the guise of "choice." Sometimes the obvious needs to be stated. Without a doubt, an Ethical Concerns section in the medical records is long overdue. However, we need to wake up and grasp the reality surrounding us if such a noble proposal is to have its full and rightful impact.

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IN RESPONSE: These two letters are linked by the observation that my proposal to create a special section in the medical record for ethical concerns is only a preliminary step toward making moral issues more central to the care of the ill. I heartily concur with that judgment and hope that such an addition might be part of a more comprehensive reevaluation of how to better identify and address patient's ethical issues. Drs. Drehmer, White, and Schuster appropriately identify crucial educational interventions and rewards that would, if widely adopted, reenforce the empathy of health care providers. Aside from such measures, a philosophical reorientation is also required. By asserting other guiding principles (1, 2) to balance the role of autonomy in medical ethics (3), the general fiduciary responsibilities of physicians for their patients would be enhanced. Fundamental to that responsibility is helping to identify moral questions and then to assist patients in finding responsible answers. This is the rationale of my proposal.

Dr. Baumgartner either misunderstood me or has identified an ambiguity: In emphasizing the lacuna of addressing ethical concerns of more ordinary cases, I did not mean to ignore those that are obviously morally laden. Transplantation and reproduction technologies bring with them, by their very nature, obvious moral issues, which must be directly addressed. These require no special attention in the sense of being identified; indeed, if anything, they require greater attention.

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Fiction as Resistance

I was a writer before I was a doctor. From an early age I was concerned with suffering and understanding, and I often turned to stories for solace. I loved stories long before I knew they were an essence of good doctoring—shared stories that bring solace, understanding, and healing to others. During summers in high school and college, I worked as a toll collector on the Rip Van Winkle Bridge, and I asked for the midnight-to-eight shift so that I could read. I remember two summers when I went through all the Russians, in those pre-dawn, quiet moments in my warm booth over the Hudson feeling a sense of connection with Dostoevsky, Tolstoy, Chekhov, and Turgenev. Love and death. My early answers to the question, "What is healing?" came from these stories. I still have a piece of an envelope on which I copied part of a letter Chekhov wrote to an editor who had criticized his story "Ward Number Six": "The best of writers are realistic and describe life as it is, but because each line is saturated with the consciousness of its goal, you feel life as it should be in addition to life as it is, and you are captivated by it" (1).

Life as it should be in addition to life as it is. Without realizing it until many years later, this would become the motor of my writing.

I began writing in 1966 when I was a Rhodes scholar at Oxford University. I viewed my time at Oxford not only as a chance to continue my fascination with science—the function of the brain in learning—but also to try to become a writer. I enrolled in a Doctor of Philosophy degree in physiology that aimed to decipher the neurophysiology of memory, but the experiments of which boiled down to a daily challenge of teaching cockroaches to lift their legs. I also started writing—plays, poems, and short stories. Almost 3 years later, after one of those fateful 1960s' road trips to Morocco over Christmas of 1968 involving camel auctions, olive harvests, belly dancers, *kif*, and a fateful meditation at an oasis of copper sulfate and date palms in the Sahara called *Le Source Bleu de Mesqui*, I returned to Oxford realizing that I didn't want to be a scientist, I wanted to be a writer. Unfortunately, my draft board disagreed. I wasn't ready to become an expatriate writer, and so I faced the choice between Vietnam and Harvard Medical School. I realized that if I depended on my writing for my livelihood, I wouldn't be able to write what I wanted—I'd probably wind up in television or film. I chose Harvard. Medicine would be my meal ticket. Somehow I would find a way to write.

From the start I loved the stories I heard, from both the patients and the few humane doctors I met. I loved surgery, but where to find the time to write? When I took my first psychiatry course—taught by a great man named Leston Havens—I woke up. The stories of the psychiatric patients were outrageous and astonishing. I have notebooks filled with verbatim sessions, with ballpoint-pen sketches of patients in the wards. Maybe I would be able to understand people better, understand suffering, widen my scope, learn how to help people heal—and I'd have mornings free to write! Sign me up!

When I graduated from medical school in 1973, one wasn't required to do a medical internship to be a psychiatrist. But as a writer I had to experience it, and I wanted to learn how to really take care of people. Little did I know that the experience of being an intern would light the fire in me to write my first novel, *The House of God.*

Writing got me going and demanded I do an internship; my internship sparked my birth as a writer.

WHAT IS RESISTANCE?

I used to think that at any given point in my life I was fairly well aware of what was going on and that I was making informed choices about what to do. As I've grown older I've come to realize that, in fact, it's only later, maybe 10 years or so later, that I can see I had little or no idea of the unseen historical forces shaping me, which pushed me one way or the other. And so it was with my internship in the Beth Israel Hospital in Boston in 1973–1974, the Nixon–Watergate year.

I and my core group of fellow interns were products of the 1960s, brought up on the civil rights movement and the Vietnam War. We believed that if we saw an injustice, we could organize, take action, and change things for the better. Our generation put the civil rights laws in the books and stopped the Vietnam War. When we entered our internship, we were told to treat our patients in ways that we didn't think were humane. We ran smack into the conflict between the received wisdom of the medical system and the call of the human heart.

It was a series of moments—which I now call "*Hey wait a second!*" moments—those moments many of us experience every day when we see, hear, or feel that something is unjust, cruel, militaristic, or simply not right. We usually let these moments pass. We do nothing to resist them. But the moments came so fast and furious in the internship, they could neither be ignored nor passed by. We had been brought up to notice, to take "life as it is" and turn it on the spindle of compassionate action to make it more like "life as it should be." This is resistance.

And so we resisted. We actually did. We stuck together and used classic, nonviolent methods—including humor—to resist. Not that there weren't casualties. Some interns got suicidal, many got depressed, and a few went through transient psychoses. But we secretly treated people humanely.

I was not aware at the time that we were actively resisting the inhumanity we were immersed in. Nor was I aware of what happened in me next: I turned to fiction as resistance. I started to write *The House of God* for catharsis,

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to share with my buddies what had been the worst year of my life. I didn't even think of getting it published at first, but one thing led to another, and after seven rewrites it was, in 1978. I was so naive that I thought just about everyone would like it—after all, I was just telling the truth, with some art. The art part was inadvertently what Wallace Stevens, echoing Chekhov, had suggested that art can at best do, "things as they are are changed upon the blue guitar" (2). Until that time I had never known that I could write "funny." Yet I realized that the year had been so brutal that the only way anyone would want to read it was if it rode on humor—much as we interns had used humor to get through the actual experience. To paraphrase an apocryphal story attributed to George Bernard Shaw: "If you tell the truth, make 'em laugh, or they'll kill you." Little did I know how radical my novel was and the backlash it would create.

RESISTANCE TO WHAT?

Simply put, to brutality and inhumanity, to isolation and disconnection.

Occasionally I run into doctors of my generation—trained in the early 1970s—who say they experienced no brutality or inhumanity in their medical training. There is wide variation in medical schools and residencies, and some specialties are more humane than others. Often, the schools and programs that are less geared toward academics and more toward basic patient care are the most kind to their trainees. However, the issue of the abuse of medical students and residents has not gone away. Many articles have been published to describe the brutality of the third and fourth years of medical school and of residency (as recently as the 5 March 2002 issue of *Annals* [3–5]). If a particular doctor can't identify with the hazards, she or he is either remarkably lucky or remarkably insensitive—that is, in pathologic denial.

As one illustration of the brutality and inhumanity, and to further understand the link between stories in medicine and stories in fiction, let me cite a common example: the delivery of bad news to a dying patient. At one point in my internship, I had a patient with metastatic breast cancer whom the surgeons had taken to the operating room, opened up, and then closed again without doing anything—the situation was hopeless. When the patient came back to the medical ward, no one had told her anything about what had happened in surgery. I—like Roy Basch, the intern–narrator of *The House of God*—was reluctant to go into her room and made the excuse to my resident that "It's not my job, it's her private doctor's job, or her surgeon's." In reality, that's as far as it went. I believe that one of the nurses finally told her the news.

But in the novel, something else happens. The resident, called "The Fat Man," offers to do it. Roy describes the scene from the doorway:

> I watched him enter her room and sit on the bed. The woman was forty. Thin and pale, she blended with the sheets. I pictured her spine X rays: riddled with cancer, a honeycomb of bone. If she moved too suddenly, she'd crack a vertebra, sever her spinal cord, paralyze herself. Her neck brace made her look more stoic than she was. In the midst of her waxy face, her eyes seemed immense. From the corridor I watched her ask Fats her question, and then search him for his answer. When he spoke, her eyes pooled with tears. I saw the Fat Man's hand reach out and, motherly, envelop hers. I couldn't watch. Despairing, I went to bed. (6)

Later that same night, returning to the ward after an admission, Roy glances into the room again: "Fats was still there, playing cards, chatting. As I passed, something surprising happened in the game, a shout bubbled up, and both the players burst out laughing" (7).

This scene never happened in my reality as an intern. In fact, in those days there was never once any information taught to us on dealing with a dying patient or giving bad news. Rather, everyone but a few brave doctors and nurses was complicit in avoiding meaningful contact with these poor, doomed people. In retrospect, this is why I wrote the scene, to resist the inhumanity toward these patients. I started with fact—my avoidance—then imagined what "should" have been done and put it in terms of the imagined Fat Man. In this way the reality of medical practice can filter into and through creative imaginations to fiction and then, in the reality of the text, serve as a guideline in understanding not only how things are but how things should be. This is an example of how to resist the inhumanity of medical practice, through fiction.

The way we were as doctors was reflected in the way I wrote about it, and then the writing reflected back on the way we—and others—could have been, and should have been, as doctors. It is much like what Tolstoy concluded in his essay "What is Art?": "Art is a human activity consisting in this, that one man consciously by means of certain external signs hands on to others feelings he has lived through, and that others are infected by these feelings and also experience them" (8). Notice that Tolstoy says, "hands on to others *feelings* he has lived through. . . ." He is not referring to a transfer of information or knowledge; he is talking about an infection by feeling. Much medical training is about information and knowledge and less about traveling the more difficult path of feeling. I believe it's crucial for doctors to stay with the feeling, listen feelingly, and not turn away from the pain and suffering in patients and themselves. There is one shining difference between knowledge and understanding: We doctors may forget knowledge, but we never forget what we understand. We understand through feeling. Think back to those vivid memories of our first patients in medical school, the ones we really "let in" and "felt with."

The connection, then, between narrative and practice is mutually shared feeling. I believe that this connection can offer doctors some way of understanding the stories we hear, read, and tell. This understanding can help us reach our own individual vision of how we "should be" as physicians.

HOW TO RESIST?

From three decades of meeting with medical students, doctors, nurses, and other allied health professionals all over the world, I have been encouraged to think about how to resist the inhumanities in medicine in more specific ways. I've come up with a few basic suggestions. We must:

1. Learn our trade, in the world. We doctors have to be competent, to be compassionate. If we're not panicked about doing a procedure or being with a patient, we will really be able to listen to, and attend to, the person we are with. In addition, we have to be aware of the world surrounding us and our patients. I would guess that we as complicit citizens are causing more cancers than we as doctors are curing. That patient of ours is never *only* that patient—that patient is also the spouse; the family; the community; the toxins in the local air, water, and earth; and the world. Medicine is part of life, not vice versa.

2. Beware of isolation. Isolation can be deadly; connection heals. Many recent studies have shown the beneficial effects of good connections between caregivers and patients, patients and families, and patients and friends. Much attention is now being paid to things that were once thought "alternative" and that we are starting to describe as "the healing environment." Good connection is at the root of it. The hospitals I trained in and wrote about were both large medical hierarchies. In these "power-over" systems, someone always has power over you, and you have power over someone else. The pressure of authority—the dominant group—comes down on people from above, and those of the subordinate group tend to scatter. The result is that interns and residents risk getting isolated. They may become isolated from each other, leading to depression and suicide, cruel actions and insanity. And each may also *get isolated from his or her authentic experience of the medical system itself*—each may start to think "*I* am crazy" rather than "*This* is crazy." And isolation—as when an intern commits suicide—can mean death. As an intern said to me, "How can we care for patients, man, if'n nobody cares for us?" The cycle of abuse goes on. The only real threat to the power of the dominant group—a power that may be based on the hierarchical lines of authority, on race, gender, class, ethnicity, or sexual preference—is the *quality of the connection among the members of the subordinate group.* Isolation is deadly; connection heals. Stick together.

3. Speak up. When we notice injustices and cruelties in the medical system, we must speak up. Speaking up not only is necessary to call attention to the wrongs of the system, *speaking up is essential for our survival as human beings.* If we see something and say nothing, we may gradually be torn apart. But large hierarchical systems are expert at retaliation. Speaking up alone is dangerous. We must stick together, and speak up with others.

4. Resist self-centeredness. Or, to put it another way, learn empathy. How do we learn to see, in our patients, ourselves? How do we learn in doctor–patient interactions to transform our role from "power-over" to "power-with"? How do we play our part in those moments that heal, those moments of what I call mutual empathy—when not only do we see the patient clearly, and the patient sees us clearly, but *each of us senses the other feeling seen?* Those moments in which you can almost hear the "*click*" of healthy connection? These are healing moments, and not just in my specialty, psychiatry. Think of a surgeon discussing with a patient whether or not to have an operation. In the old days, a paternalistic surgeon might say, "I'm telling you, you need this operation." Lately this has changed to "I've given you all the information, and now *you* have to decide." A few surgeons have gone further toward a more mutual approach, saying, "What are we going to decide to do?" Note that using "we" does not take the decision away from the patient; rather, it lets the patient know that the surgeon is *with* him or her in the decision-making process. Such a statement empowers not only doctor and patient but also *the relationship* between doctor and patient.

How to learn empathy? Try living through suffering with someone—*really* living through—an opportunity we doctors have every day. Try life.

CONCLUSION

The healing essence of narrative is not in the "I" or the "you," but in the "we." J.D. Salinger, in *The Catcher in the Rye*, has Holden Caulfield say: "What really knocks me out is a book that, when you're all done reading it, you wish the author that wrote it was a terrific friend of yours and you could call him up on the phone whenever you felt like it" (9). Like the Tolstoy quote, this suggests that what "works" in fiction is the writer's ability to fashion a "self-with-other" experience, the ability to create a sense of mutual relationship with the reader. How is this done? The writer, through his or her particular qualities of being-in-relationship, cannot help but express these qualities of relationship in the writing; the writing carries these qualities to the reader; this sparks a sense of mutuality between reader and writer, a sense of relationship based on shared understanding.

As I've gotten older, I understand how conditioned I am to see the world in terms of "either/or," "I," or "you"—the adversarial world-view that makes lawyers rich and science, in its narrow view, seem triumphant. From time to time I've been offered glimpses of what now seems a more authentic world, the world of "and" (which includes and affirms "either/or") and the world of "we" (which includes and affirms "I" and "you"). This is the world in which subatomic particles can *only* be known not in themselves but in their relationships with other particles; it's also the world in which I cannot see you or me with clarity and understanding unless I can see the connection between us. Sometimes I find myself in a shift from seeing people only as individuals to seeing the connections between people that mirror and inform each person. I've come to see healthy growth not so much as the growth of a self, but as the growth of a self-in-connection. Mutuality is a more authentic description of humans and nature than dichotomy.

Finally, a word about how my specialty, psychiatry, plays into my lifelong quest to write a fiction of resistance. My question in psychiatry has always been, "How do people change?" In my novel *Mount Misery*, the sequel to *The House of God*, Roy Basch tries to describe what heals. At the end of the year he is having a difficult time in a therapy session with a patient. She is a troubled young woman who has always made him feel inadequate.

> "Terrific," she said to me sarcastically, putting me down. She looked sullenly into her lap.
>
> In the past I might have gotten angry at her, but suddenly I understood. The issue wasn't me, or her, but us. The "we" in the room, which seemed so solid right then that you could shape it, yet so ephemeral that it was the unseen historical forces shaping you . . .. My job right then was to hold this "we," this connection with her, hold it for both of us. That was my job as a doctor. To use my experience with others who had suffered and my vision born of that experience to bring someone who is out on the edge of the so-called 'sick' into the current of the human. To take what seems foreign in a person and see it as native. This is healing. This process is what the healing process is. This is what I signed up for, years ago. This is what good doctors do. We are with people at crucial moments of their lives, healing. How hard it had gotten . . . to get back to authentic suffering, authentic healing. How much we have lost. (10)

The great themes of fiction are love and death. Death is always a theme in medicine. So too, I would argue, in its many spirits, is love. And one of those spirits is resistance. Love and death. How lucky we are.

Samuel Shem
Boston, MA 02199

Note: Samuel Shem is the author's pen name. The author's real name is Stephen J. Bergman.

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Bioterrorism: Guidelines for Medical and Public Health Management

Henderson DA, Inglesby TV, O'Toole T, eds. 244 pages. Chicago: American Medical Assoc; 2002. $29.95. ISBN 157947280X. Order phone 800-621-8335 or at www.amapress.com.

Field of medicine: Infectious diseases, microbiology, and public health.

Format: Softcover book.

Audience: Primary care physicians, emergency medicine personnel, infectious diseases physicians, medical microbiologists, hospital epidemiologists, infection control practitioners, public health officials, and lawyers addressing public health issues.

Purpose: To guide medical and public health efforts following a biological weapons attack on civilian populations.

Content: Before the anthrax attacks of 2001, the Working Group on Bioterrorism published widely read consensus statements on the medical and public health aspects of the biological weapons likely to cause the greatest disruption, illness, and death—anthrax, smallpox, botulism, plague, tularemia, and viruses causing viral hemorrhagic fever. This book provides a useful compilation of those statements (each has been updated to integrate information published after its initial release). In addition, five cases from the anthrax attacks of 2001 are described, and there is a thoughtful discussion of the utility, feasibility, ethics, and legality of one often-discussed public health measure, large-scale quarantine. Other chapters address the importance of understanding biological weapons and the new challenges posed by bioterrorism for U.S. medicine.

Highlights: The consensus statements are excellent, readable summaries of the existing literature that clearly delineate what we know and what we need to know. They are of value to experts and to those seeking information about these subjects for the first time. The individual case descriptions are poignant and communicate the complexity and severity of an illness that few have experienced firsthand.

Limitations: This reader would have liked access to the figures and tables for use in presentations. Specific laboratory protocols and procedures must be found in other sources.

Related reading: This volume, along with past and future articles in *Morbidity and Mortality Weekly Report* (*MMWR*) and supplements to *MMWR*, should keep health care workers abreast of current official recommendations.

Reviewer: Elias Abrutyn, MD, Drexel University College of Medicine, Philadelphia, Pennsylvania.

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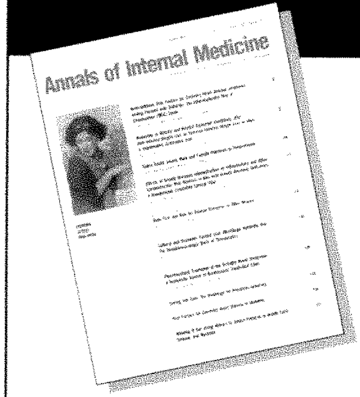

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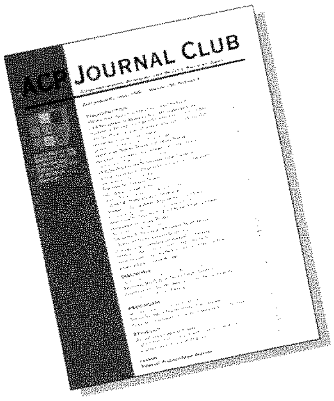

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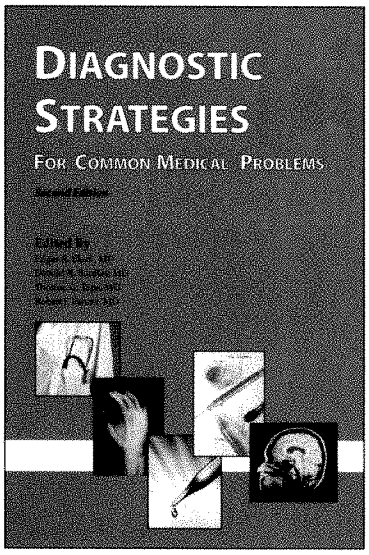

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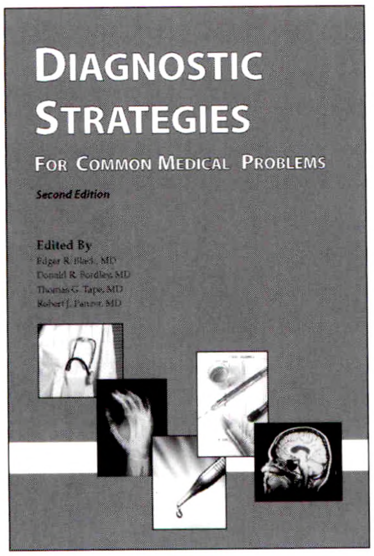

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Compared with placebo, unrefined echinacea provided no detectable benefit or harm in college students who had the common cold.

Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States 947

G. Ostapowicz, R.J. Fontana, F.V. Schiødt, A. Larson, T.J. Davern, S.H.B. Han, T.M. McCashland, A.O. Shakil, J.E. Hay, L. Hynan, J.S. Crippin, A.T. Blei, G. Samuel, J. Reisch, W.M. Lee, and the U.S. Acute Liver Failure Study Group

Acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent causes of acute liver failure. The cause of liver failure and coma grade at admission were associated with outcome. Although transplantation may improve patient survival, most patients did not need it or could not get it.

Residual Venous Thrombosis as a Predictive Factor of Recurrent Venous Thromboembolism 955

P. Prandoni, A.W.A. Lensing, M.H. Prins, E. Bernardi, A. Marchiori, P. Bagatella, M. Frulla, L. Mosena, D. Tormene, A. Piccioli, P. Simioni, and A. Girolami

Residual venous thrombosis after discontinuing anticoagulation is an important risk factor for recurrent thromboembolism. Assessing residual venous thrombosis with ultrasonography may help clinicians to identify patients who need prolonged anticoagulation.

BRIEF COMMUNICATION

Prevalence of Liver Disease in a Population of Asymptomatic Persons with Hepatitis C Virus Infection 961

A. Alberti, F. Noventa, L. Benvegnù, S. Boccato, and A. Gatta

Up to 40% of asymptomatic persons with hepatitis C virus infection have histologically active and progressive hepatitis. The severity of liver disease correlates with abnormal alanine aminotransferase levels and increases with age.

ACADEMIA AND CLINIC

Credentialing Complementary and Alternative Medical Providers 965

D.M. Eisenberg, M.H. Cohen, A. Hrbek, J. Grayzel, M.I. Van Rompay, and R.A. Cooper

This article describes models for health care credentialing of chiropractors, acupuncturists, naturopaths, massage therapists, and other complementary and alternative medical (CAM) practitioners. It also suggests a strategy of CAM provider credentialing for use by physicians, health care administrators, insurance companies, and national professional organizations.

UPDATE

Update in Infectious Diseases 974

B. Lorber

This Update covers terrorist threats to the health of the public, new approaches to some familiar clinical problems, newly recognized disorders, novel treatments for infectious diseases, HIV infection, and infectious complications of treatment for other illnesses.

REVIEW

Novel Insights in the Congenital Long QT Syndrome 981

X.H.T. Wehrens, M.A. Vos, P.A. Doevendans, and H.J.J. Wellens

The congenital long QT syndrome is a potentially life-threatening condition caused by mutations in genes encoding cardiac ion channels. The increasing understanding of the mechanisms responsible for these conditions should lead to genotype-specific therapy.

HISTORY OF MEDICINE

Smallpox Manifestations and Survival during the Boston Epidemic of 1901 to 1903 993

M.R. Albert, K.G. Ostheimer, D.J. Liewehr, S.M. Steinberg, and J.G. Breman

The authors describe clinical manifestations of smallpox during Boston's last major epidemic (1901–1903) and analyze factors associated with survival among patients admitted to one hospital.

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Editorial

Echinacea for the Common Cold: Can Alternative Medicine Be Evidence-Based Medicine? 1001

R.B. Turner

The study by Barrett and colleagues in this issue is a valuable contribution to the literature on echinacea because it addresses many shortcomings of earlier studies. Although the study was carefully done and the results are clear, their work is not likely to end the discussion about the efficacy of echinacea for the common cold.

On Being a Doctor

The Healing Touch 1003

L. Opatrny

He reached out to grasp my resting hand. Then, suddenly, this man, who had until now spoken and moved so very slowly, started rapidly and vigorously rubbing my hand between both of his. "To warm you up, doctor. My wife also gets cold when she's tired. This has always helped her," Mr. B. explained, never taking his eyes off his task. "You should be sleeping to take care of yourself instead of old men like me," he added.

On Being a Patient

Trust 1004

S.C. Durso

I was struck by the irony of this doctor–patient relationship. In the office our relationship was conventional. He was the heart patient and I was his doctor. The marsh was different. Here Ezra and I were in each other's hands.

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J. Coulehan

Cockroach 1006

J. Coulehan

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Annals of Internal Medicine

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The Appendix for the Information for Authors is published in the first issues of January and July and includes information on manuscript format, style, article components, and publication.

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Annals of Internal Medicine | ARTICLE

Treatment of the Common Cold with Unrefined Echinacea

A Randomized, Double-Blind, Placebo-Controlled Trial

Bruce P. Barrett, MD, PhD; Roger L. Brown, PhD; Kristin Locken, BA; Rob Maberry, BA; James A. Bobula, PhD; and Donn D'Alessio, MD

Background: Echinacea preparations are widely used to treat the common cold.

Objective: To assess the efficacy of dried, encapsulated, whole-plant echinacea as early treatment for the common cold.

Design: Randomized, double-blind, placebo-controlled community-based trial.

Setting: University of Wisconsin—Madison, Madison, Wisconsin.

Participants: 148 registered students with common colds of recent onset.

Intervention: An encapsulated mixture of unrefined *Echinacea purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) taken in 1-g doses six times on the first day of illness and three times on each subsequent day of illness for a maximum of 10 days.

Measurements: Severity and duration of self-reported symptoms of upper respiratory tract infection.

Results: No statistically significant differences were detected between the echinacea and placebo groups for any of the measured outcomes. Trajectories of severity over time were nearly identical in the two groups. Mean cold duration was 6.01 days in both groups as a whole, 5.75 days in the placebo group, and 6.27 days in the echinacea group (between-group difference, −0.52 day [95% CI, −1.09 to 0.22 days]). After controlling for severity and duration of symptoms before study entry, sex, date of enrollment, and use of nonprotocol medications, researchers found no statistically significant treatment effect (adjusted hazard ratio, 1.24 [CI, 0.86 to 1.78]). Multivariable regression models assessing severity scores over time failed to detect statistically significant differences between the echinacea and placebo groups.

Conclusion: Compared with placebo, unrefined echinacea provided no detectable benefit or harm in these college students who had the common cold.

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See editorial comment on pp 1001-1002.

The common cold is one of the world's most prevalent illnesses. Upper respiratory tract infection, characterized by rhinosinusitis, pharyngitis, or tracheobronchitis, is caused by a wide array of agents. While rhinovirus is most common, coronavirus, respiratory syncytial virus, adenovirus, parainfluenza, and influenza virus all play important roles (1–4). Effects on health, well-being, and productivity are significant. Although patients with such complications as asthmatic bronchospasm, bacterial sinusitis, otitis media, streptococcal pharyngitis, or pneumonia might benefit from medical intervention, few if any treatments have proven effective for community-acquired colds (5–10).

Preparations made from plants of the genus *Echinacea* are widely used for the prevention and treatment of colds (11–13). Various whole-plant preparations and extracts made from the flowers, leaves, stems, and roots of *E. purpurea*, *E. angustifolia*, and *E. pallida* are sold worldwide. Hundreds of scientific studies, mostly German, have detailed echinacea's botanical, chemical, and pharmacologic characteristics and its clinical effects (14–19).

There is no clear consensus about whether echinacea can benefit human health. Randomized, controlled trials have focused on the prevention or treatment of colds. Five such trials of prevention (four of which have been published) reported that echinacea had little effect in reducing the incidence of natural colds (20–23; Calabrese C. Personal communication). The findings of the highest-quality study (21) are consistent with a 10% to 15% reduction in relative risk. Results of an induced-cold trial have been reported as negative but are consistent with a benefit of 10% to 15% (24). The 11 published treatment trials are somewhat more positive (25–35), and systematic reviews have been cautiously optimistic (13, 14, 18, 36, 37). Reported benefits have ranged from a 40% to 50% reduction in severity (31) and duration (29) of symptoms in studies with major methodologic limitations to more modest reductions of 10% to 30% in the most recent studies (25, 27, 28). All studies to date have had important limitations, including lack of objective validated outcome measures, lack of description and verification of random allocation and concealment procedures, limitations related to sample size and power, and limited generalizability.

METHODS

In spring 1999, we conducted a randomized, double-blind, placebo-controlled community-based trial evaluating the efficacy of an encapsulated whole-plant echinacea preparation used as early treatment for the common cold. Participants with early cold symptoms were randomly assigned (with allocation concealed) to echinacea treatment or placebo and were followed with self-reported duration and severity measures for the duration of illness, up to 10 days. All participants provided informed consent before the study, and the University of Wisconsin Medical School human subjects committee approved the protocol.

Shaklee Tecnica (Pleasanton, California) provided the echinacea and placebo preparations. Each active capsule contained a dried mixture of *E. angustifolia* root (50% [123 mg]), *E. purpurea* root (25% [62 mg]), and *E. pur-*

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Context

Echinacea is an herbal therapy that is widely used to treat the common cold, but there is no consensus about its effectiveness.

Contribution

This randomized, controlled trial compared a capsule form of *Echinacea purpurea* herb and root and *E. angustifolia* root with placebo in 148 college students with symptoms of the common cold. Echinacea had no effect on the duration or severity of cold symptoms.

Implications

This particular form of echinacea provides no benefit for common cold symptoms in young, healthy adults. It will be necessary to perform similar careful studies of other echinacea preparations, which could differ from the preparation used in this study.

–The Editors

purea herb (25% [62 mg]). Echinacea capsules also contained thyme (49 mg) and peppermint (31 mg) to disguise taste and flavor, as well as citric acid (3 mg) as a preservative. The placebo capsules contained 333 mg of alfalfa. Each participant was given a bottle containing 132 capsules and was instructed to take four capsules per treatment dose six times during the first 24 hours of the study, and three times each day thereafter until symptoms resolved, for a maximum of 10 days. Each four-capsule dose totaled 1 g. Thus, the dose schedule was 6 g of echinacea on the first day and 3 g on each subsequent day.

Participants were recruited from 4 February 1999 until 20 May 1999 from the University of Wisconsin—Madison student population. Advertisements throughout the student community (posters, newspaper advertisements, and e-mail messages) asked respondents to call a cellular telephone held by a research assistant at the first sign of cold or flu-like symptoms. Callers were screened by telephone and were invited to meet with a research assistant if eligible, usually within a few hours of the initial call. At the enrollment interview, the research assistant described the study protocol, obtained informed consent, gathered baseline data, and provided instruction on the paper questionnaire and the Web-based survey instrument.

To be included in the study, participants were required to be at least 18 years of age, to answer "Yes" to the question "Do you believe that you are coming down with a cold?", to report at least 2 of 15 listed cold symptoms (at least 1 of which had to be specific to the respiratory tract), and to be apparently able and willing to adhere to the study protocol. Participants were excluded if they reported having any listed symptom for more than 36 hours; were pregnant; were currently using antibiotics, antihistamines, or decongestants; had specified chronic diseases (autoimmune disease, chronic bronchitis, HIV infection, lupus, rheumatoid arthritis); or had a history of asthma or allergic rhinitis and corresponding symptoms (itchy eyes, sneezing, wheezing) at the time of enrollment.

Randomization was designed so that each participant would have a 50% chance of assignment to placebo or echinacea. The Investigational Drug Service of the University of Wisconsin Hospitals randomized and sequentially labeled 200 bottles containing echinacea or placebo, using a random-number generator (Microsoft Excel, Microsoft Corp., Redmond, Washington) and a balanced blocks-of-four design. Each sequentially enrolled participant received the next sequentially numbered bottle of capsules. The placebo and echinacea capsules were indistinguishable to study personnel and to the participants. Allocation to echinacea or to placebo was concealed from participants and from the investigational team until all data had been collected, entered, and cleaned.

Primary outcomes were defined prospectively as severity and duration of self-reported symptoms. Duration was defined as the number of days from study enrollment to the last day before the participant answered "No" to the question, "Do you think that you are still sick today?" Symptom severity was measured daily on nine-point Likert scales. The 15 symptoms assessed were dry cough, productive cough, cough interfering with sleep, sore throat, scratchy throat, hoarseness, runny nose, plugged or stuffy nose, sneezing, headache, fever, sweats, muscle aches, feeling "run down," and loss of appetite. Each reported symptom was rated on a nine-point Likert severity scale with the following label: 1 (very mild), 3 (mild), 5 (moderate), 7 (severe), and 9 (extreme). Global severity of illness ("How sick do you feel today?") was assessed by using a similar nine-point scale.

For each day of the trial, participants were asked to fill out both a paper and an electronic version of the questionnaire. The electronic version was adapted to a Web page format (www.fammed.wisc.edu/samplecold). Blinded data were downloaded and inspected periodically throughout the trial. The parallel data collection system enabled us to verify the time and date of response, protecting against errors from retrospective assessments. It also protected against data entry error and missing data and allowed comparison of data reported in electronic and paper formats.

Participants were in contact with the enrolling research assistant by telephone and e-mail throughout the study. They returned for an exit interview upon study completion. Adherence was assessed by pill counts (from bottles returned at the end of the study) and by the daily questionnaire (which asked the participants whether they had taken their pills and how many pills they had taken). Adverse effects were monitored each day and at the exit interview.

Our study was designed to have 150 participants, providing at least 80% power to detect a benefit of 2 days' duration or an average reduction of two points in severity. These prospective power calculations (38, 39) assumed variance similar to that observed in cold studies (9, 10) and benefits similar to those reported in previous echinacea trials (27–31). The minimal clinically important benefit for the common cold has not been determined (40, 41). However, research on other illnesses suggests that an average two-point reduction in severity on a nine-point scale or a 2-day reduction in duration would be clinically significant (42–46).

A symptom-dimension measurement model was constructed by using structural equation modeling techniques (47, 48, 51). From the pool of 15 symptoms, 14 items fit neatly into four symptom dimensions. Loss of appetite was an infrequent symptom that contributed insignificantly and was therefore dropped. The four dimensions and their associated reliability coefficients, calculated by using the method of Dillon and Goldstein (48), were cough (0.794), throat (0.668), nasal (0.663), and fever and aches (0.753). Reliability coefficients estimate the proportion of variability that is attributable to participants' symptoms rather than to measurement error (45, 49, 50). Five covariates were investigated as possible confounders: 1) duration of symptoms before study entry, 2) severity of illness at enrollment, 3) date of enrollment (seasonal or etiologic agent effect), 4) use of nonprotocol medications, and 5) sex.

Statistical Analysis

We considered all available data in our analysis. Methods included simple inspection, frequency analysis, analysis of variance, and multivariable analysis. Confidence intervals were constructed for all outcomes. A simple sum of the 15 symptom scores was selected as an overall severity marker for use in regression models. Changes over time in the summed severity score were explored by using the general linear mixed model for repeated measures (51). Individual symptom scores and dimensional severities were similarly explored by using mixed modeling approaches (52). Bootstrap resampling was used to calculate means and confidence intervals for duration (53). A Cox multivariable proportional hazards regression model (54) for cold duration was used to control for potential confounding. The lack of time trends in the Schoenfeld residuals supports the proportional hazards assumption (55). The five potential confounders previously noted were included in all multivariable models. Statistical analyses were done by using SAS software (SAS Institute, Inc., Cary, North Carolina).

Figure 1. **Randomization and patient flow.**

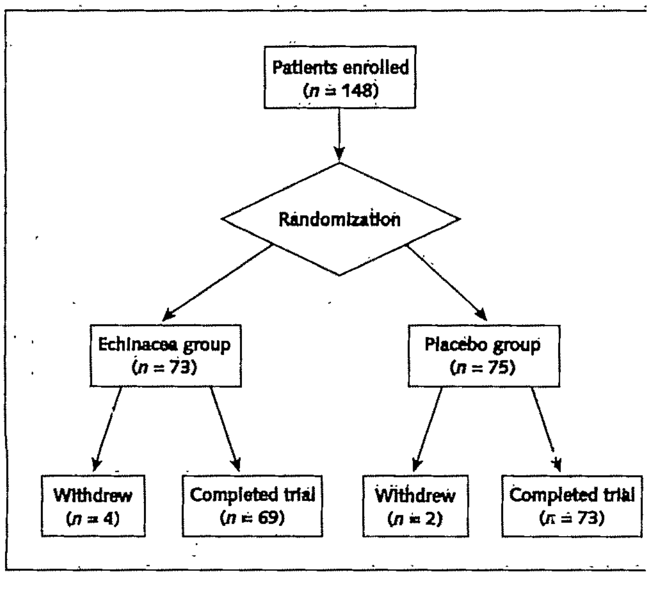


Table. **Characteristics of Study Participants**

Characteristic	Echinacea Group	Placebo Group
Participants entering study, *n*	73	75
Participants completing protocol, *n*	69	73
Mean age ± SD, *y*	20.8 ± 2.4	21.0 ± 3.4
Women, *n (%)*	50 (72)	48 (66)
Current use of tobacco, *n (%)*	15 (22)	15 (21)
Nonwhite ethnicity, *n (%)*	4 (5.8)	4 (5.5)
Participants who had taken echinacea before, *n (%)*	30 (43)	28 (38)

Role of the Funding Sources

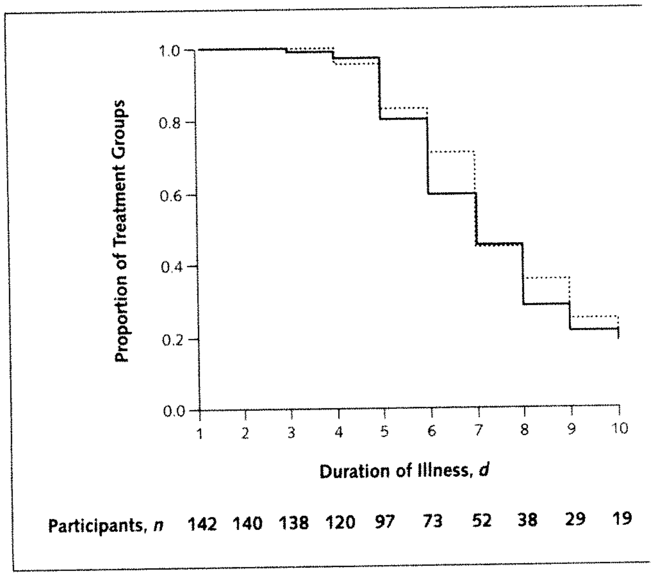
The U.S. Department of Health and Human Services and the National Institutes of Health provided funding to Dr. Barrett during the study. Shaklee Tecnica provided monetary support for project costs and provided the study materials, but had no role in the design, conduct, or reporting of the data or in the decision to submit the manuscript for publication.

RESULTS

Of 148 enrolled participants, 142 (69 in the echinacea group and 73 in the placebo group) completed our protocol successfully (Figure 1). Characteristics of the study sample are shown in the Table. We did not record the number of eligible persons who called the research center but were unwilling to participate in the study; however, it was clear that most eligible callers were enrolled. The mean time from onset of the first recognized symptom to study enrollment was 27 hours.

A total of 853 person-days of illness were reported. Six participants withdrew, 2 in the placebo group (1 because of feeling too sick and 1 for undisclosed reasons) and 4 in the echinacea group (2 because of being too sick to follow the protocol, 1 because the capsules tasted bad and were difficult to swallow, and 1 for undisclosed reasons). In the echinacea group, 27 participants reported taking nonprotocol medications compared with 25 participants in the placebo group. Of the 142 participants who completed the study, 10 (5 in each group) reported having had at least one symptom for more than 36 hours at enrollment. For these 10 persons, the duration from first symptom to enrollment was 36 to 40 hours ($n = 2$), 45 to 48 hours ($n = 6$), 72 hours ($n = 1$), or 168 hours ($n = 1$). Because these protocol violations were discovered after the trial ended, we

Figure 2. **Illness duration.**



The dotted line represents the echinacea group; the solid line represents the placebo group.

chose to include data from these 10 persons in our results. For the six persons lost to follow-up, no postenrollment data were available.

After unblinding in July 1999, samples of the echinacea formulation were sent to three independent laboratories for analytic testing. Dr. Rudolph Bauer (Institut fuer Pharmazeutische Biologie, Heinrich-Heine-Universitaet Duesseldorf, Duesseldorf, Germany) analyzed our formulation and found that it contained 0.26% echinoside; 0.77% cichoric acid; and 0.82% alkamides, including 0.42% dodecatetraenoic acid isobutylamide by weight (15, 56, 57). Industrial Labs (Denver, Colorado) analyzed our product using a standardized method developed by their methods validation program and reported that it contained 0.20% echinoside, 0.84% cichoric acid, 0.03% chlorogenic acid, and 0.33% cafeolytartaric acid. Dr. Joseph Ringer at Paracelsian, Inc. (Langmuir Laboratories, Ithaca, New York), used cell culture and simulated digestion methods with bioequivalent doses of our study product to demonstrate macrophage activation and elevated levels of tumor necrosis factor. The equivalent of our first-day dose increased the mean level (±SD) of tumor necrosis factor from 189 ± 23 ng/L to 3679 ± 154 ng/L, while the equivalent of our subsequent daily dose increased the mean level to 2347 ± 66 ng/L. Together, these three analyses demonstrate that our product contained substantial quantities of phytochemicals as active constituents (14, 15).

Pill counts and daily computerized monitoring demonstrated protocol adherence. An overall adherence rate of 92% was calculated by dividing the number of pills missing from the bottles by the number that should have been missing based on the protocol. On the Web-based questionnaires, nearly all of the participants reported taking their pills nearly every day during their participation in the trial.

Before the study, we conducted several informal tests of blinding. Study personnel, friends, and colleagues could not distinguish between placebo and echinacea capsules. At the exit interview, we asked participants, "Do you think you were taking echinacea or placebo?" Blinding was successful: Thirty-one of 63 persons taking echinacea and 33 of 72 persons taking placebo guessed correctly ($P > 0.2$). Seven participants declined to guess.

Of the 853 person-days of illness, 546 (64%) were captured by both paper and electronic data systems. Two hundred eighty-seven person-days (34%) were captured by paper surveys alone, while 18 (2%) were accounted for solely by the computerized system. Only 2 person-days (0.2%) were not accounted for by either system. Therefore, for 142 participants documenting 853 days of illness, our data capture rate was 99.8%. In constructing the final data set, we used the computerized data whenever available because they were verified by time and date. We used data originally recorded on paper as needed.

Comparing data from the computerized and paper symptom surveys provided some evidence of instrument reliability. Responses to the question about global severity of illness were identical on 512 of the 546 days for which both instruments provided data (94% concordant, 6% discrepant). Of 34 discrepancies, 29 were off by one point on the nine-point Likert scale and 5 were off by two points. Comparing computer and paper responses to the 15 specific-symptom questions also yielded high levels of concordance. Of 8190 answers, 7777 (95%) were concordant and 413 (5%) were classified as data discrepancies. Of these, 293 were off by one point on the nine-point scale, 68 were off by two points, 27 were off by three points, 17 were off by four points, 7 were off by five points, and 1 was off by six points.

We did not detect a difference in cold duration between the echinacea and placebo groups. Among the 142 participants completing our protocol, durations ranged from 2 to 10 days, with a median of 6 days and a mean (±SD) of 6.01 ± 2.34 days (**Figure 2**). The mean duration was 5.75 days in the placebo group and 6.27 days in the echinacea group (difference, −0.52 day [95% CI, −1.09 to 0.22 days]). Therefore, 0.22 day is the largest potential echinacea-related benefit in duration that would be statistically compatible with our results. After adjustment for the five potential confounders, Cox multivariable regression found no statistically significant treatment effects on duration (adjusted hazard ratio, 1.24 [CI, 0.86 to 1.78]), with the trend toward longer duration in the echinacea group.

We did not detect any significant differences in symptom severity between the echinacea and placebo groups. **Figures 3** and 4 depict daily mean severities and 95% CIs for the symptoms assessed. The group sizes decrease over time, following recovery from illness. A general linear mixed model of the unweighted summed severity score (controlling for the five potential confounders) did not reveal any statistically significant differences between the echinacea and placebo groups. Duration of symptoms before study entry, date of enrollment, and sex were not statistically significant. Although use of nonprotocol medications and severity of illness at enrollment had independent effects on subsequent severity, neither potential confounder could account for the lack of observed treatment effects.

Models of individual symptoms and of symptom dimensions (again controlling for the five confounders) similarly failed to demonstrate treatment effects. Although uncontrolled linear models of the cough dimension indicated slightly more rapid recoveries in the placebo group, these differences were not apparent in more complex models that better represented dimension severity over time. More severe illness in the placebo group on the first day of the trial, before treatment was initiated, appeared to explain the trends favoring placebo in the linear models. There were no statistically significant differences between echinacea and placebo in scaled responses to the global severity question, "How sick do you feel today?" Mean scores of responses to this question are shown in **Figure 3**.

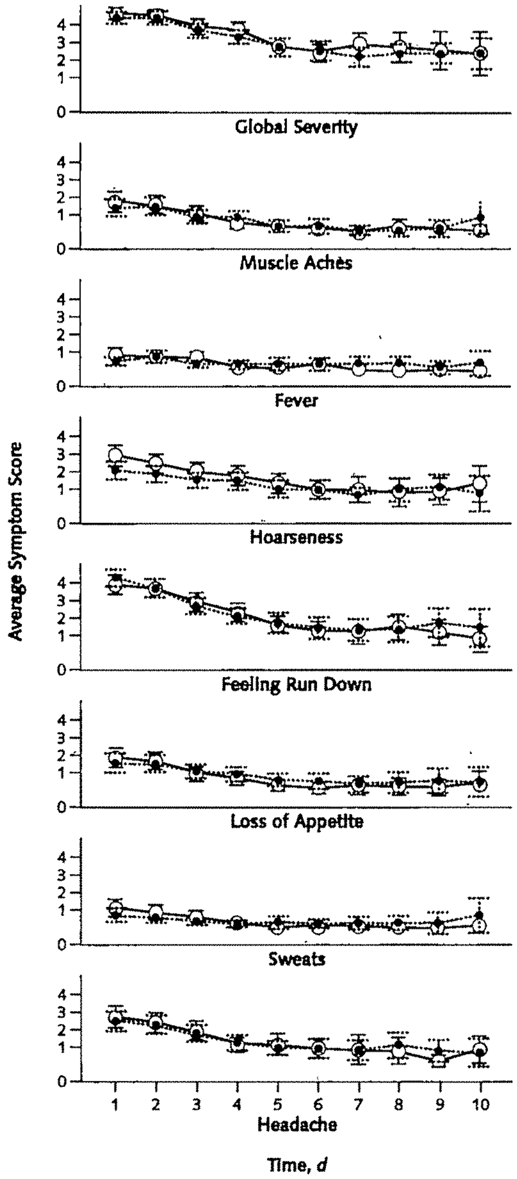
In our analysis, we included all available data from the 142 persons who completed the study protocol. We collected no useful data for the six participants who were enrolled but were lost to follow-up. Regression results described earlier and mean values portrayed in **Figures 2, 3,** and 4 do not include data for these six participants and therefore do not represent an intention-to-treat analysis. However, to assess whether data from the six persons who withdrew could have affected our results, we performed an analysis that imputed symptom-recovery trajectories for each missing participant based on the average of 1000 randomly selected trajectories. This analysis yielded results very similar to those described earlier (data not shown).

Specific adverse effects were reported on the daily questionnaires 22 times by 15 participants who completed the study (9 times by 7 participants in the placebo group and 13 times by 8 participants in the echinacea group). In the echinacea group, sleeplessness, heartburn, nausea, stomachache, and upset stomach were each reported by one participant and bad taste was noted by three participants. In the placebo group, stomachache was noted by three participants and nausea, belching, thirst, and abdominal pain with diarrhea were each noted by one participant. Reported adverse effects were therefore not statistically different between the echinacea and placebo groups.

DISCUSSION

We consider the results of this trial to be negative. We did not detect the effect size for which the trial was powered (2 days' duration and two points in average severity on a nine-point scale) or any potentially significant trends. All differences noted between the echinacea and placebo groups could be explained by natural variability in the underlying symptoms measured. Our results do not support a benefit of echinacea in the treatment of common cold symptoms. However, we do not believe that our trial should be the last word on echinacea. Our results contradict the current published evidence, and our trial had limitations. Previous trials have reported statistically significant symptomatic benefit with echinacea taken early in the

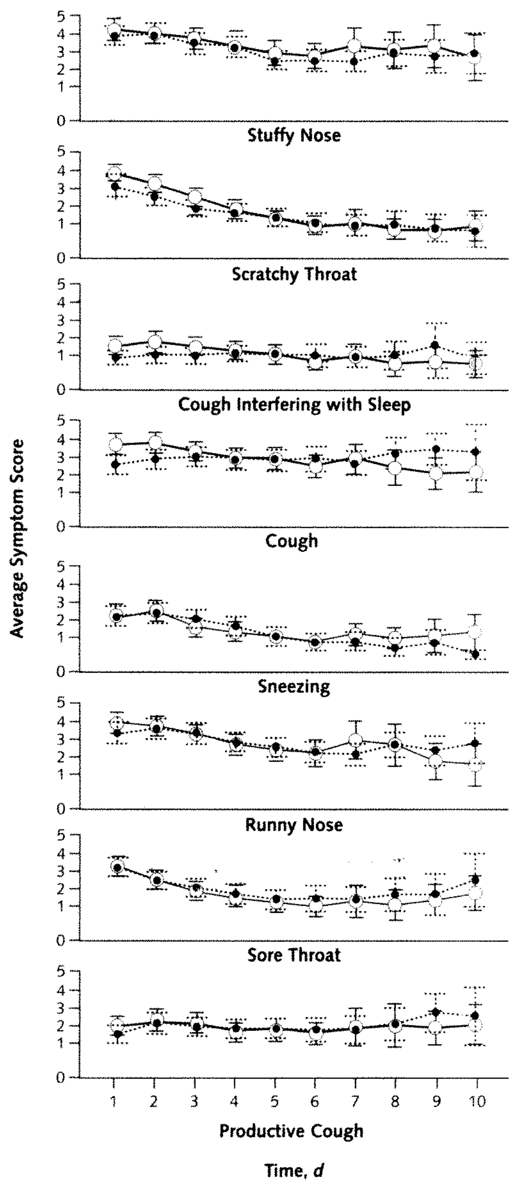
Figure 3. **Mean severity of global and general symptoms.**



	1	2	3	4	5	6	7	8	9	10
Echinacea group, *n*	69	68	67	60	51	36	31	22	16	11
Placebo group, *n*	73	72	71	60	46	37	21	16	13	8

Dotted lines represent the echinacea group; solid lines represent the placebo group. Error bars represent 95% CIs. Although 95% CIs indicate the uncertainty of the severity of symptoms, they should not be used to compare symptom severity on any particular day.

Figure 4. **Mean severity of specific cold symptoms.**



Echinacea group, *n*	69	68	78	60	51	36	31	22	16	11
Placebo group, *n*	73	72	71	60	46	37	21	16	13	8

Dotted lines represent the echinacea group; solid lines represent the placebo group. Error bars represent 95% CIs. Although 95% CIs indicate the uncertainty of the severity of symptoms, they should not be used to compare symptom severity on any particular day.

course of an acute upper respiratory tract infection (27–29, 31–35). These trials, especially those by Brinkeborn (28) and Henneicke-von Zepelin (27) and colleagues, are similar to our trial in quality but report positive results. In addition, published systematic reviews have concluded that there may be benefit to early echinacea treatment (13, 18, 36, 37). There are several possible reasons for this discrepancy. The positive results of previous trials could be due to bias or chance, and the widespread belief in echinacea's benefit could be entirely false.

However, our trial had several limitations that should temper confidence in its negative results. First, the specific echinacea preparation used in our trial, a dried, encapsulated mixture of unrefined *E. angustifolia* root and whole-plant *E. purpurea*, has not been tested previously and may be ineffective because of bioavailability or phytochemical constituents. Previous trials with positive results have used extracts rather than whole-plant products (25, 27–35), and some have combined echinacea with other plant species (27, 32–35). Because phytochemical constituents vary among botanical species, growing conditions, plant part, and extraction method, it is possible that one preparation would provide benefit while another would not.

Second, the type of people included in our study, healthy undergraduate college students, may not gain much benefit from echinacea. Previous trials have tended to include older adults and have sometimes sought to include those with histories of frequent colds. There is a prevailing notion that echinacea provides greatest benefit to persons who are immunocompromised, a state often evidenced by frequent colds or other viral illnesses. We made no effort to seek out such persons.

Third, although our modest-size trial would have detected a large benefit, an effect size of 5% or 10% could easily have been missed among the natural variability of symptoms found in persons with community-acquired colds. From a health measurement perspective, it should be emphasized that our study was limited because we used self-reported symptoms as primary outcomes (44, 45, 58, 59). Subjective self-assessments can introduce several potential biases.

To date, there are no validated instruments for assessing the common cold (10, 40, 41). We have begun refining and validating our instrument (60), but although its face validity is strong, construct validity has not been demonstrated. It should also be noted that we monitored participants for a maximum of 10 days and therefore do not know the frequency of longer illnesses. Finally, five people in each of our study groups received echinacea after having symptoms for 36 hours, which may have masked a benefit of echinacea given earlier in cold presentation. Future research is necessary to provide more definitive evidence about whether echinacea is an effective treatment for the common cold.

From University of Wisconsin—Madison, Madison, Wisconsin.

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ARTICLE

Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States

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Background: Because acute liver failure is rare, related data have been sparse. Studies have suggested that viral hepatitis is the most common underlying cause of this condition.

Objective: To describe the clinical features, presumed causes, and short-term outcomes of acute liver failure.

Design: Prospective cohort study.

Setting: 17 tertiary care centers participating in the U.S. Acute Liver Failure Study Group.

Patients: 308 consecutive patients with acute liver failure, admitted over a 41-month period.

Measurements: Detailed clinical and laboratory data collected during hospitalization, including outcome 3 weeks after study admission.

Results: 73% of patients were women; median age was 38 years. Acetaminophen overdose was the most common apparent cause of acute liver failure, accounting for 39% of cases. Idiosyncratic drug reactions were the presumptive cause in 13% of cases, viral hepatitis A and B combined were implicated in 12% of cases, and 17% of cases were of indeterminate cause. Overall patient survival at 3 weeks was 67%. Twenty-nine percent of patients had liver transplantation, and 43% survived without transplantation. Short-term transplant-free survival varied greatly, from 68% for patients with acetaminophen-related liver failure to 25% and 17% for those with other drug reactions and liver failure of indeterminate cause, respectively. Coma grade at admission appeared to be associated with outcome, but age and symptom duration did not.

Conclusions: Acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent apparent causes of acute liver failure. Apparent cause and coma grade at admission were associated with outcome. Although transplantation may improve patient survival, it was unavailable or unnecessary for most patients.

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Acute liver failure is characterized by severe and sudden liver cell dysfunction leading to coagulopathy and hepatic encephalopathy in previously healthy persons with no known underlying liver disease (1). Sometimes termed *fulminant hepatic failure*, acute liver failure is thought to affect approximately 2000 persons per year in the United States (2). This catastrophic illness can rapidly progress to coma and death from cerebral edema and multiorgan dysfunction (2, 3).

Over the past 30 years, the most frequently identified cause of acute liver failure has been viral hepatitis, especially hepatitis B but also hepatitis A and, in tropical populations, hepatitis E (4–8). Smaller numbers of cases have been related to drug-induced liver injury and other causes (9). The frequency of identified causes of acute liver failure has varied greatly worldwide. A very high prevalence of suicidal overdoses of acetaminophen (73%) has been recorded in the United Kingdom (10), and no cases of acetaminophen-related disease have been observed in developing countries (7).

Until recently, only limited data have been available on the cause and outcome of acute liver failure in the United States, presumably because of the relative rarity of the condition, referral patterns in North America, and lack of a centralized data registry (11–14). The U.S. Acute Liver Failure Study Group was formed in 1997 as a consortium of liver centers interested in better defining causes and outcomes of acute liver failure. The primary aim of the current study was to prospectively describe, with emphasis on the role of transplantation, the causes of acute liver failure and short-term outcomes of patients with this condition who presented to participating liver centers between 1998 and 2001. Our secondary aim was to compare presenting clinical features and liver transplantation in patients with acute liver failure related to acetaminophen hepatotoxicity, other drugs, indeterminate factors, and other causes.

METHODS

Between January 1998 and May 2001, a 41-month period, 308 patients 15 years of age or older were enrolled from 17 tertiary care liver centers around the United States, all but one of which has a liver transplantation program. The local institutional review board of each center approved the study. All enrolled patients met entry criteria for acute liver failure: the presence of coagulopathy (prothrombin time > 15 seconds or international normalized ratio ≥ 1.5) and any hepatic encephalopathy within 26 weeks of the first symptoms without previous underlying liver disease (15). Informed consent was obtained from patients' next of kin before enrollment, according to the guidelines of local institutional review boards. On the basis of records of patients considered for enrollment but ex-

Context

Acute liver failure is a catastrophic condition affecting about 2000 persons in the United States each year.

Contribution

Among 308 consecutive patients with liver failure admitted to 1 of 17 referral centers between 1998 and 2001, acetaminophen overdose (39%) and idiosyncratic drug reactions (13%) were the most common cause of disease. Sixty-seven percent of patients were still living 3 weeks after presentation (44% without liver transplantation and 23% after transplantation). Survival was associated with cause of liver failure (persons with acetaminophen overdose fared best) and depth of coma at presentation.

Implications

Drug toxicities cause most cases of acute liver failure in the United States. Cause and depth of coma at presentation predict patient outcomes.

–The Editors

cluded because of lack of informed consent or other reasons, more than 65% of eligible patients were enrolled.

Under code to protect confidentiality, each center provided detailed demographic, clinical, laboratory, and outcome information for all enrolled patients. Hepatic coma was graded on a standard scale of I to IV, as described elsewhere (1, 2). Etiologic diagnoses, which were made at each study center, were based on accepted diagnostic criteria circulated to all investigators. These criteria involved history; laboratory values; imaging studies; and, in some cases, histopathologic characteristics. Acute liver failure was considered to be of indeterminate cause when extensive clinical, radiographic, and laboratory evaluation (including toxicology screens and serologic markers for viral hepatitis A, B, and C and antinuclear and anti–smooth-muscle antibodies) was inconclusive. Investigators tested and searched for other viruses by using RNA methods as clinically indicated, but these results were not uniformly available. Clinical guidelines for patient management, although determined at each site, were uniform (16).

Candidacy for liver transplantation was determined at individual centers according to the guidelines of the United Network of Organ Sharing. Shortly after patients were admitted to the study, an initial case report form was completed and forwarded to the central study site (University of Texas Southwestern Medical Center, Dallas, Texas). In addition, an outcome case report form detailing the hospital course and final laboratory results not available at admission was completed within 3 weeks of discharge, death, or transplantation. Outcome end points, which were determined 3 weeks after study admission, included liver transplantation, death, and survival without transplantation. Case report forms were checked for missing values and inconsistencies; queries were sent to the participating centers, and corrections were made at the data coordinating center. All data were then entered into an Access database (Microsoft Corp., Redmond, Washington). Annual site visits by researchers from the data coordinating center confirmed the accuracy of the data.

Statistical Analysis

Results are expressed as medians and ranges. Statistical significance was not used in the analysis because the data were descriptive.

Role of the Funding Sources

The funding sources had no specific role in the design, conduct, or reporting of the study.

RESULTS

Demographic Characteristics and Clinical Data

Of the 308 patients with acute liver failure, 224 (73%) were women. The median age of the group was 38 years (range, 15 to 78 years); women were older than men (39 years vs. 32.5 years). Two hundred twenty-seven patients (74%) were white, 31 (10%) were Hispanic, 29 (9%) were African American, 10 (3%) were Asian, 5 (2%) were Native American, and 6 (2%) were of other ethnic backgrounds. Extensive variation was seen in the median duration of symptoms (6 days [range, 0 to 74 days]) and jaundice (2 days [range, 0 to 61 days]) before encephalopathy onset. Coma grade at study admission was relatively equally distributed (**Table 1**). Forty percent of patients had a serum creatinine concentration of 177 µmol/L or greater ($\geq$2.0 mg/dL), and 14% had acidosis (arterial pH $<$ 7.30). Nearly half of patients (44%) acquired a culture-proven infection. Most patients (260 [84%]) were referred from other hospitals, and the remainder were admitted directly to the tertiary care centers.

Causes of Acute Liver Failure

The **Figure** displays the presumed cause of acute liver failure and the outcome data for all study patients. Acetaminophen overdose was the most commonly implicated reason for acute liver failure, accounting for 120 patients (39%). The median dosage of acetaminophen ingested was 13.2 g/d (range, 2.6 to 75 g/d), and 99 of 120 patients (83%) had ingested more than 4 g/d (the maximum package recommendation). Among these 120 patients, 44 (37%) were considered to have ingested acetaminophen with suicidal intent (single ingestion with suicide attempt admitted) and 68 (57%) had accidental toxicity (many ingestions for pain relief without suicidal intent). In 8 patients (7%), the reason for overdose could not be determined.

Idiosyncratic drug reactions were deemed responsible for another 40 cases of acute liver failure (13%). Hepatitis A and B infection led to 14 cases (4%) and 22 cases (7%), respectively. Presumptive diagnoses of ischemic hepatitis ("shock liver"), autoimmune hepatitis, Wilson disease, and

Table 1. **Characteristics of Patients at Admission according to Presumed Cause of Acute Liver Failure***

Variable	Presumed Cause of Acute Liver Failure			
	Acetaminophen	**Other Drugs**	**Indeterminate**	**All Others**
Patients, *n*	120	40	53	95
Median age (range), *y*	36 (19–76)	41 (20–65)	38 (15–76)	43 (15–78)
Women, *n (%)*	95 (79)	29 (72)	32 (60)	68 (72)
White ethnicity, *n (%)*	108 (90)	23 (58)	35 (66)	61 (64)
Survived without transplant, *n (%)*	82 (68)	10 (25)	9 (17)	31 (33)
Survived with or without transplant, *n (%)*	87 (73)	28 (70)	34 (64)	58 (61)
Received transplant, *n (%)*	7 (6)	21 (53)	27 (51)	34 (36)
Coma grade at study admission, *n*				
I	33	8	14	21
II	27	15	14	29
III	35	14	15	21
IV	25	3	10	24
Maximum coma grade, *n*				
I	18	7	14	17
II	35	10	10	24
III	31	20	14	22
IV	36	3	15	32
Mean symptom duration (range), *d*	3 (0–32)†	15.5 (2–74)	23 (0–67)	10 (0–64)
Mean jaundice duration (range), *d*‡	1 (−3 to 12)	12 (−1 to 59)	12 (0–61)	4 (−5 to 42)
Mean value of mean arterial pressure, *mm Hg*	87 (41–130)	92 (67–118)	84 (34–133)	88 (52–133)
Mean platelet count (range), × *1000 cells/mm³*	125 (16–699)	154 (36–376)	129 (14–462)	148 (28–424)
Mean prothrombin time (range), *s*	28.5 (15.0–135)	22.5 (15.2–86.6)	23.7 (15.1–151.4)	26.8 (15.0–106)
Mean INR (range)	2.8 (1.5–44.4)	2.4 (1.5–10.9)	2.7 (1.5–24.8)	2.7 (1.5–26.1)
Mean serum bicarbonate level (range), *mmol/L*	21 (2–35)	23 (7–37)	23 (9–31)	23 (7–36)
Mean ALT level (range), *U/L*	4310 (136–17 670)	574 (88–5380)	947 (32–10 660)	1060 (3–12 533)
Mean AST level (range), *U/L*	4333 (59–28 870)	636 (127–3673)	858 (93–14 626)	1003 (50–21 925)
Mean bilirubin level (range)				
µmol/L	74 (5–592)	345 (127–852)	419 (17–742)	215 (22–1026)
mg/dL	4.3 (0.3–34.6)	20.2 (7.4–49.8)	24.5 (1.0–43.4)	12.6 (1.3–60.0)
Mean creatinine concentration (range)				
µmol/L	168 (44–928)	88 (27–460)	106 (35–619)	133 (35–2210)
mg/dL	1.9 (0.5–10.5)	1.0 (0.3–5.2)	1.2 (0.4–7.0)	1.5 (0.4–25.0)
Mean arterial pH	7.41 (6.94–7.65)	7.48 (7.26–7.63)	7.46 (7.10–7.59)	7.44 (7.12–7.81)

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

† Some patients with accidental acetaminophen overdose had symptoms for a long period.

‡ Jaundice developed after onset of encephalopathy in some patients.

the Budd–Chiari syndrome accounted for 17 (6%), 13 (4%), 8 (3%), and 5 (2%) cases, respectively. Six patients with pregnancy-associated acute liver failure were listed as having acute fatty liver ($n = 2$), the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome ($n = 3$), or eclampsia ($n = 1$). Acute liver failure was attributed to cancer (metastatic carcinoma or lymphoma) in 4 patients and to another cause (heat stroke, sepsis, or giant-cell hepatitis) in 6 patients. Fifty-three cases (17%) of indeterminate cause were equally divided among the 12 centers (median cases per center, 4.5 [range, 1 to 9]).

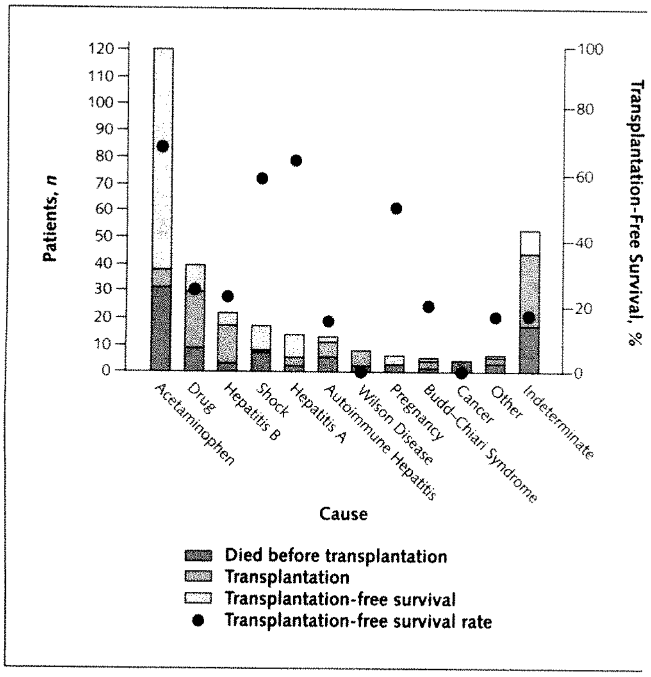
Comparison of Clinical and Laboratory Features by Presumed Cause

Table 1 shows between-group differences in clinical and laboratory data at admission, based on presumed cause of acute liver failure. All groups had a similar preponderance of women. Patients with acetaminophen-related liver failure and those with indeterminate liver failure were younger than patients with liver failure that was drug induced or related to other causes. White persons were overrepresented in the acetaminophen group compared with the other three groups. Patients with acetaminophen-related disease had shorter disease duration; higher serum alanine aminotransferase, aspartate aminotransferase, and creatinine levels; and lower bilirubin levels and arterial pH. The drug-induced and indeterminate groups had longer disease duration, lower alanine aminotransferase levels, and higher bilirubin levels. The groups did not differ significantly in other measures of disease severity at presentation (for example, coma grade, mean arterial pressure, prothrombin time, or international normalized ratio).

Outcomes

Short-term outcomes were assessed 3 weeks after study admission (Figure). Most patients (286 of 308 [93%]) had a definitive outcome (death, transplantation, or hospital discharge) at 3 weeks. Overall survival was 67% (207 of 308 patients). One hundred thirty-two patients (43%) survived without transplantation. One hundred thirty-five patients were listed for transplantation, and 89 (66% of listed patients, 29% of the total study group) received a liver graft. Seventy-five patients who received transplants survived for at least 3 weeks (short-term survival, 84%). Causes of death for the 101 patients who died were cere-

Figure. **Presumed causes and outcomes in 308 patients with acute liver failure.**



bral edema, multiorgan failure, sepsis, cardiac arrhythmia or arrest, and respiratory failure. Thirty patients died awaiting a graft, and 47 died but had not been listed for transplantation. The median time from transplantation listing to actual transplantation was 3.5 days (range, 1 to 42 days), and median time to death after admission was 5 days (range, 2 to 21 days).

Short-term outcomes varied according to the presumed cause of acute liver failure (**Figure**, **Table 1**). For patients with acetaminophen overdose, hepatitis A virus infection, shock liver, or pregnancy-related acute liver failure, short-term survival without transplantation was 50% or greater. Patients whose liver disease was of indeterminate cause or was presumed to be related to drugs other than acetaminophen, hepatitis B virus infection, autoimmune hepatitis, Wilson disease, the Budd–Chiari syndrome, or cancer had lower rates of short-term transplant-free survival (<25%) (**Figure**). Transplantation was performed in only 6% of the acetaminophen group compared with 53% of the drug-induced group, 51% of the indeterminate group, and 36% of the "other cause" group. Fifty-six of 120 patients with acetaminophen-related liver failure (47%) fulfilled transplantation criteria. However, only 32 (57%) were listed for transplantation; the remaining patients were excluded for psychosocial reasons (for example, psychiatric disease or substance abuse) or because of medical contraindications (for example, sepsis or cerebral edema). While short-term survival without transplantation was lower in the drug-induced and indeterminate groups, overall survival was similar in all groups (acetaminophen group, 73%; drug-induced group, 70%; indeterminate group, 64%; "other cause" group, 61%) (**Figure**, **Table 1**). Rates of overall survival, transplant-free survival, and transplantation were independent of sex (data not shown).

Age Comparisons

Because age is thought to affect the outcome of acute liver failure, we analyzed outcomes by decades of life. The peak age group for patients with acute liver failure was 26 to 35 years, and the number of patients in each age group gradually decreased with increasing age. Overall survival remained relatively unchanged for all age groups (between 63% and 77%) except for those older than 65 years of age. These patients had poor survival (33%), but the group was relatively small ($n = 15$).

Symptom Duration

Since symptom duration has also been used to predict outcome, we used the methods described by O'Grady and colleagues (15) to stratify patients with non–acetaminophen-related liver failure. Hyperacute failure was classified as 7 or fewer days of symptoms before onset of hepatic encephalopathy, acute failure was classified as 8 to 28 days of symptoms, and subacute failure was classified as more than 28 days of symptoms. Information on symptom duration was available for 178 of the 188 patients with non–acetaminophen-related liver failure (95%). As shown in **Table 2**, transplantation was used more frequently and transplant-free short-term survival was lower in the subacute group. Serum aminotransferase levels were highest and bilirubin levels were lowest in the hyperacute group.

Role of Coma Grade at Admission

At study admission, 161 patients (52%) presented with grade I or II hepatic coma. Among these patients, 84 (52%) survived without transplantation for 3 weeks. In contrast, of 147 patients who presented with grade III or IV hepatic coma, 48 (33%) survived 3 weeks without transplantation. The transplantation rate was 29% for patients with grade I or II coma and those with grade III or IV coma, whereas overall rates of short-term survival in these groups were 77% and 56%, respectively. Short-term transplant-free survival was 87%, 35%, 18%, and 38%, respectively, for patients with presumed acetaminophen overdose, drug reactions, liver failure of indeterminate cause, or liver failure of other causes who presented with grade I or II coma and was 50%, 12%, 16%, and 27%, respectively, for patients who presented with grade III or IV coma. The corresponding overall rates of short-term survival were 88%, 70%, 79%, and 66% and 57%, 71%, 48%, and 56%.

DISCUSSION

This study is one of the first to prospectively characterize a large number of patients with acute liver failure from several U.S. tertiary care centers, all but one of which perform liver transplantation. Earlier studies have been small, retrospective, or limited to single academic centers

Table 2. **Characteristics of Patients with Non–Acetaminophen-Related Acute Liver Failure according to Symptom Duration before Onset of Hepatic Encephalopathy***

Variable	Hyperacute Liver Failure	Acute Liver Failure	Subacute Liver Failure
Patients, *n*	53	83	42
Mean age (range), *y*	39 (15–78)	42 (15–72)	41.5 (17–65)
Women, *n (%)*	40 (75)	51 (61)	31 (74)
White ethnicity, *n (%)*	33 (62)	55 (66)	28 (67)
Cause of liver failure, *n*			
Autoimmune disorder		10	3
Budd–Chiari syndrome	1	3	1
Drugs	6	21	11
Hepatitis A	4	7	3
Hepatitis B	11	8	1
Indeterminate	12	20	16
Cancer	1	1	2
Other	1	2	2
Pregnancy	5	1	
Shock	11	5	1
Wilson disease	1	5	2
Survived without transplant, *n (%)*	16 (30)	27 (33)	6 (14)
Survived with or without transplant, *n (%)*	27 (51)	57 (69)	27 (64)
Received transplant, *n (%)*	16 (30)	32 (39)	25 (60)
Mean platelet count (range), × *1000 cells/mm³*	119 (14–386)	155 (19–452)	132 (24–462)
Mean prothrombin time (range), *s*	24.3 (15.3–100)	26.1 (15.0–106)	23.7 (15.2–151)
Mean INR (range)	2.3 (1.5–15.5)	2.9 (1.5–15.5)	2.5 (1.5–15.5)
Mean ALT level (range), *U/L*	1753 (3–12 533)	972 (11–7603)	373 (26–6430)
Mean AST level (range), *U/L*	1569 (52–20 000)	863 (50–21 925)	430 (127–8850)
Mean bilirubin level (range)			
µmol/L	183 (17–920)	373 (31–1026)	416 (26–992)
mg/dL	10.7 (1.0–53.8)	21.8 (1.8–60.0)	24.3 (1.5–58.0)
Mean creatinine concentration (range)			
µmol/L	150 (27–557)	106 (35–2210)	106 (44–583)
mg/dL	1.7 (0.3–6.3)	1.2 (0.4–25.0)	1.2 (0.5–6.6)

* Hyperacute liver failure = 0–7 days of symptoms before encephalopathy onset; acute liver failure = 8–28 days of symptoms before encephalopathy onset; subacute liver failure = >28 days of symptoms before encephalopathy onset. Laboratory values reported are those at admission. ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

over many years (11–14, 17). Our previous study, which included 295 patients who developed acute liver failure from 1994 to 1996, was limited because it provided only minimal retrospective information on demographic features, presumed cause, and outcome (18). Our present study was also limited because it provided detailed information only from tertiary care centers. In that sense, our data set does not represent U.S. patients overall and is subject to biases regarding referral for transplantation. Patients who were elderly, had underlying malignant disease, may have had milder disease, or may have had other issues precluding transplantation were probably underrepresented. Because our selection criteria were coagulopathy and encephalopathy, only the most severely ill patients were included. The overall outcome for the conditions studied would have been considerably better if all hospitalized patients had been included.

We observed a much higher frequency of presumed acetaminophen overdose–related hepatotoxicity (39%) than have previous reports. We included all cases evaluated at the tertiary care centers as long as informed consent could be obtained. It is likely that the proportion of acetaminophen-related cases in our earlier retrospective study (20%) was an underrepresentation; that study included only data from transplantation databases, and many patients with acetaminophen toxicity are not listed for transplantation. No acute liver failure attributed to acetaminophen had been reported in three small U.S. series, totaling 129 cases, before the advent of transplantation in the early 1980s (11–13). In one more recent study from a single large transplantation center in 1983 to 1995, acetaminophen was listed as the presumed cause of injury in 19% of cases (14). The apparent increase in the proportion of acetaminophen cases in our study might be partly explained by a decreasing incidence of other diseases, such as viral hepatitis. Nevertheless, our findings may represent a real increase in the incidence of acetaminophen-related acute liver failure as observed in U.S. transplantation centers.

Acetaminophen is the most widely used nonprescription analgesic in the United States. In the Third National Health and Nutrition Examination Survey (19), 76% of Americans reported using a nonprescription product in the previous month, and 36% specified acetaminophen. There is very little evidence of liver injury when acetaminophen is used according to package recommendations. Nevertheless, acetaminophen is a common putative cause of severe liver injury because of its recognized dose-related hepatotoxicity; its easy availability; and possibly other cofactors, such as alcohol use and starvation (20–22). Unlike in the United Kingdom, more than half of our patients with presumed acetaminophen overdose were believed to have overdosed accidentally rather than during a suicide attempt. However, most of our patients (83%) exceeded the daily maximum recommended dose, and the median dose in our series was more than three times that value. It should be stressed that only the most severely ill patients, those who have usually taken the largest overdoses or who have had a long delay before initiation of antidote treatment, develop acetaminophen-related liver failure (23).

Our patients with acute liver failure related to acetaminophen were as ill as those with failure related to other causes. However, many more patients in the former group survived (73%), and very few received liver transplants (6%). Patients with acetaminophen-related liver failure have the best chance of spontaneous recovery with supportive care; however, 43% in our study were not considered for transplantation because of medical contraindications and psychosocial reasons (alcohol or other substance abuse; repeated suicide attempts; and, in two cases, lack of funding). Despite the relatively good outcome of patients with acetaminophen-related liver failure, 33 of our patients with this type of disease died (28% of all patients in the acetaminophen group and 11% of patients admitted to the study). The even higher proportion of acetaminophen-related cases in Europe (24–26) has led to legislation limiting the quantity of acetaminophen available without a prescription (27–29). In light of these findings, our observation of an apparent increase in prevalence of severe liver injury due to acetaminophen overdose bears close scrutiny.

Idiosyncratic drug reactions appeared to cause 13% of cases of acute liver failure. Two of the drugs prominently implicated, bromfenac and troglitazone (four cases each), have been withdrawn by the U.S. Food and Drug Administration (30, 31). Isoniazid was thought to be responsible for five cases of acute liver failure in our study. However, despite its toxicity, it remains first-line therapy for tuberculosis worldwide (7).

The importance of idiosyncratic drug reactions is reflected in the overall poor outcome for patients with this type of liver failure; only 25% recover spontaneously once hepatic encephalopathy is present. Patients with acute liver failure of indeterminate cause made up 17% of our study group and were equally represented across the study sites. Whether another hepatotropic virus or unknown drug exposures were present in these patients remains to be determined. No specific features suggest that these cases had a unique cause. It is likely, however, that some patients ingested a toxin but had no history to suggest this and that others contracted a virus that may have acted as the etiologic agent.

A striking finding in our study is that nearly three quarters of U.S. patients with acute liver failure are women. The proportion increased from 54% in our previous retrospective study (18) to 73% in the present study. In earlier U.S. studies of acute liver failure, between 56% (13) and 63% (11, 14) of cases occurred in women. The reasons for the preponderance of women in our series have not been elucidated. A real increase over an interval of less than 4 years seems unlikely. Causes of acute liver failure that are specific to women, such as those related to pregnancy or breast cancer, were involved in only a small number of our cases. Female preponderance was present in all groups in our study, so a simple increase in the total number of acetaminophen-related cases, in which women predominate, cannot account for these differences. The possibility of a selection bias related to greater availability of relatives for informed consent was not borne out by our records of patients for whom consent could not be obtained. Whether women are innately more susceptible to acute liver failure or are taking more kinds of prescription and nonprescription drugs and are therefore at higher risk remains to be determined (19).

The overall short-term survival in our study (67%) is much higher than that previously observed in the United States. In the three small studies done in the pretransplantation era, survival rates were between 3% and 18% (11–13). Two more recent studies, our retrospective study (18) and the large single-center study (14), yielded short-term survival rates of 25% and 14% without transplantation and 49% and 41% with transplantation, respectively. By comparison, our current series yielded a short-term transplant-free survival rate of 43%, and only 29% of our patients received a liver graft. These more favorable results seem to reflect both an increase in patients with acetaminophen-related disease, who are more likely to have survived 3 weeks without transplantation, and a substantial role for liver transplants in management of acute liver failure.

The pretransplantation hospital stays of those who received a liver graft (median, 3.5 days) and those who died while on the waiting list (median, 5 days) were very similar, indicating the limited time span in which transplantation is possible. In all, 30 patients (10%) died awaiting a graft despite being listed in the top recipient category (United Network of Organ Sharing Status 1). Accurate prognostic tests for determination of outcome are lacking. Another 16 patients, 35% of those who were listed for but did not receive transplants, recovered after being placed on the transplantation list. Given the shortage of available organs and the high cost of transplantation, new therapies for acute liver failure are urgently needed.

Previous European studies have suggested that acute liver failure is more likely to be fatal in patients older than 40 years of age and those younger than 10 years of age (24). We confirmed that most cases of acute liver failure were in younger patients (26 to 45 years). However, the rate of overall survival was not worse for adult patients through age 65 years, and only a few of our patients were older than 65 years of age. The spontaneous survival rate was highest for patients 26 to 35 years of age and 36 to 45 years of age; however, because these age groups also had the highest numbers of acetaminophen-related cases, this higher rate was not unexpected (data not shown). Our study does not suggest that age was an important determinant of outcome. However, because of a selection bias toward fitness for transplant candidacy, many older patients are probably excluded from referral to liver transplantation centers.

Symptom duration is considered to be a major variable in determining the prognosis of patients with acute liver failure (15). Paradoxically, patients with hyperacute onset of hepatic encephalopathy (≥8 days of symptoms before coma) have been considered to have a better prognosis than those with acute (8 to 28 days of symptoms) or subacute (>28 days of symptoms) onset (15, 32). However, when we excluded patients with acetaminophen-related disease from the hyperacute group (Table 2), the results did not differ from those of the acute group. The subacute group still had the lowest likelihood of spontaneous survival. Overall survival did not differ among the groups, possibly because the rate of transplantation was higher (60%) in the subacute group. In addition to the predicted poorer survival in the subacute group, which led to earlier listing for transplantation, the slower disease evolution may have increased the likelihood of receiving a liver graft (33). In keeping with previous studies (24), our results suggest that coma grade at admission may be an important determinant of outcome and emphasize the importance of early transfer to an intensive care setting. Better prognostic models are needed to more accurately predict outcome, preventing transplantation in those who will survive without it and allowing the procedure in those who otherwise have no hope of survival.

Acute liver failure, although rare, remains a rapidly progressive and frequently fatal condition. Estimates of overall incidence cannot be derived from our study. Treatment is generally supportive (in the absence of an antidote such as *N*-acetylcysteine for acetaminophen overdose), and infection and cerebral edema remain the leading causes of death. In the United States, most liver injury is presumably due to medications (acetaminophen overdose and idiosyncratic drug reactions) and may therefore be preventable. Clinicians should be aware of the rapidity with which liver injury evolves and the possible dire consequences for patients who develop any degree of coagulopathy and encephalopathy. Since outcome is unpredictable, early transfer to a transplantation facility should be considered before the onset of advanced grades of coma, after which transfer becomes impossible. Further understanding of the pathophysiologic characteristics of this multisystem condition and the development of better support therapies should improve the outcome of patients with acute liver failure.

APPENDIX: U.S. ACUTE LIVER FAILURE STUDY GROUP, 1998–2001

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ARTICLE

Residual Venous Thrombosis as a Predictive Factor of Recurrent Venous Thromboembolism

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Background: The optimum duration of anticoagulant therapy after an episode of deep venous thrombosis (DVT) is controversial. Contributing to the controversy is uncertainty about whether residual venous thrombosis, as assessed by repeated ultrasonography over time, increases the risk for recurrent thromboembolism.

Objective: To determine the risk for recurrent thromboembolism in patients who have persistent residual thrombosis compared with patients who have early vein recanalization.

Design: Prospective cohort study.

Setting: A university hospital in Padua, Italy.

Patients: 313 consecutive symptomatic outpatients with proximal DVT who received conventional short-term anticoagulation.

Measurements: Ultrasonographic assessment of the common femoral and popliteal veins was performed 3 months after acute DVT in all patients and at 6, 12, 24, and 36 months in patients found to have residual venous thrombosis. Veins were considered recanalized if they were 2.0 mm or less in diameter on a single test or 3.0 mm or less in diameter on two consecutive tests. Recurrent thromboembolism was assessed during a 6-year period.

Results: The cumulative incidence of normal results on ultrasonography was 38.8% at 6 months, 58.1% at 12 months, 69.3% at 24 months, and 73.8% at 36 months. Of 58 recurrent episodes, 41 occurred while the patient had residual thrombosis. The hazard ratio for recurrent thromboembolism was 2.4 (95% CI, 1.3 to 4.4; *P* = 0.004) for patients with persistent residual thrombosis versus those with early vein recanalization.

Conclusions: Residual venous thrombosis is an important risk factor for recurrent thromboembolism. Ultrasonographic assessment of residual venous thrombosis may help clinicians modify the duration of anticoagulation in patients with DVT.

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Patients with deep venous thrombosis (DVT) of the lower extremities are usually treated with an initial course of unfractionated or low-molecular-weight heparin followed by at least 3 months of oral anticoagulant therapy. This treatment regimen reduces the risk for short-term thromboembolic complications to approximately 5% (1, 2). Although the short-term outcome of this disease has been extensively documented, only a few studies have addressed the risk for late recurrent venous thromboembolism. These studies suggest that this risk persists for years and is related to patient characteristics at initial presentation (1, 2). It has been documented that patients with continuous risk factors, such as cancer or the antiphospholipid antibody syndrome, and those with idiopathic thrombosis have a two- to threefold increased risk for recurrence compared with patients who developed a thrombotic event in association with a transient risk factor (3–5). As a consequence, longer anticoagulant treatment (up to several years) has been evaluated in patients with idiopathic DVT, with the aim of decreasing recurrences in patients with idiopathic DVT (6, 7). Although long-term anticoagulant therapy is effective in preventing recurrences, it is inconvenient and carries a risk for bleeding (8–11). It would be beneficial to further improve our ability to identify patients who are at higher risk for recurrent events.

The absolute incidence of recurrent venous thromboembolism decreases over time (3, 5). Residual thrombus mass also decreases over time in patients with proximal venous thrombosis, according to recent studies that used repeated ultrasonographic imaging (12, 13). If vein recanalization indicates a lower risk for recurrent disease, ultrasonographic imaging might help clinicians adjust the duration of oral anticoagulant therapy on an individual basis in patients who have had an episode of DVT. To estimate whether the risk for recurrent venous thromboembolism is higher in the presence of residual thrombosis, we performed repeated ultrasonography in a large number of patients with proximal venous thrombosis who were followed prospectively for up to 6 years.

METHODS

Study Design

We performed a prospective cohort follow-up study to assess the potential effect of residual venous thrombosis on the risk for recurrent venous thromboembolism in patients with a first episode of symptomatic DVT. The institutional review board of Padua University, Padua, Italy, approved the study.

Inception Cohort

All consecutive outpatients who were referred to the Department of Medical and Surgical Sciences of the University of Padua between 1993 and 1996 for clinical suspicion of a first episode of DVT and who met inclusion criteria were eligible. Inclusion criteria were proximal venous thrombosis on compression ultrasonography, absence of diseases requiring indefinite anticoagulation (such as atrial fibrillation, active cancer, chronic medical illnesses,

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Context

Doctors typically treat deep venous thrombosis with anticoagulants for 3 to 6 months to prevent recurrence. Patients at high risk for recurrence may benefit from longer treatment. Can we identify them with ultrasonography that detects persistent thrombosis?

Contribution

Three hundred thirteen patients with deep venous thrombosis had ultrasonography every 6 to 12 months for 3 years. Recurrent thromboembolism, assessed over 6 years, was more frequent among those showing persistent residual thrombosis rather than early vein recanalization.

Implications

We now need trials that evaluate prolonged anticoagulation in patients with and without residual thrombosis to see whether tailoring treatment on the basis of serial ultrasonography is beneficial.

–The Editors

or other permanent risk factors for venous thrombosis), life expectancy of more than 6 months, and ability to return to the study center for follow-up visits. Eligible patients received conventional anticoagulation (full doses of unfractionated or low-molecular-weight heparin followed by 3 months of oral anticoagulant therapy). Patients who completed the initial 3 months of treatment without a recurrent thrombotic episode and who gave informed consent were recruited for the current study.

On the basis of laboratory results and clinical characteristics, patients were divided into three categories: those who had thrombophilia, those who had secondary DVT, and those who had idiopathic DVT. Tests for thrombophilia (antithrombin, protein C or S defect, factor V Leiden mutation, prothrombin G20210 gene mutation, and lupus-like anticoagulants) were performed before anticoagulation was started or at least 2 weeks after its conclusion. On the basis of test results, patients were categorized as being with or without thrombophilia. Patients without thrombophilia were further classified as having idiopathic DVT or DVT secondary to transient risk factors, according to a standardized form for clinical data collection completed at referral. Secondary thrombosis was defined as that occurring during pregnancy or childbirth; during estrogen use for contraception or hormone replacement therapy (ongoing or interrupted for <1 month); or after recent trauma, fracture, or surgery (within <3 months). If thrombophilia screening could not be performed, patients were classified as having idiopathic or secondary DVT on the basis of clinical presentation.

Ultrasonographic Assessments

The first ultrasonographic assessment was performed 3 months after the initial event. Patients found to have residual thrombosis were scheduled for repeated assessment 6, 12, 24, and 36 months after the initial event. Independent experts who were unaware of patients' clinical details or of previous ultrasonographic findings performed assessments according to a standardized procedure. Only the common femoral vein at the saphenofemoral junction and the popliteal vein in the midpopliteal fossa were scanned for residual venous thrombosis. Vein compression was performed in the transverse plane; vein diameter was measured during maximal compression and was expressed in millimeters. Veins were considered recanalized if they were 2.0 mm or less in diameter on a single test or 3.0 mm or less in diameter on two consecutive tests. This definition was based on ultrasonographic findings from a separate group of 145 patients with proven proximal DVT who were followed prospectively at our institution in the early 1990s; fewer than 2.0% of these patients developed recurrent thromboembolism in the 2 years after vein recanalization (12).

Follow-up and Recurrent Venous Thromboembolism

All recruited patients were instructed to interrupt oral anticoagulant therapy when they were included in the current study. Patients were followed to document the incidence of symptomatic recurrent DVT or pulmonary embolism. Patients were educated about the main signs and symptoms of recurrent venous thromboembolism and received a card with the telephone numbers of the thrombosis clinic. They were instructed to return to the study center if they noted clinical manifestations suggestive of recurrent venous thrombosis (edema, redness, tenderness, pain, or swelling) in either leg or suggestive of pulmonary embolism (dyspnea, chest pain, or tachycardia). Patients were also seen at the time of ultrasonographic assessments and were contacted at least twice yearly to ascertain whether signs and symptoms had occurred. If they had, patients were invited to come to the study center for additional diagnostic procedures.

Recurrent DVT was diagnosed by compression ultrasonography, followed by ascending phlebography in case of indeterminate findings, or a strong discrepancy between clinical suspicion and negative results on ultrasonography (14). Patients with suspected pulmonary embolism had ventilation–perfusion lung scanning, which was followed by pulmonary angiography if findings were inconclusive (15). Fatal pulmonary embolism was diagnosed on the basis of autopsy findings or the opinion of an independent physician.

Statistical Analysis

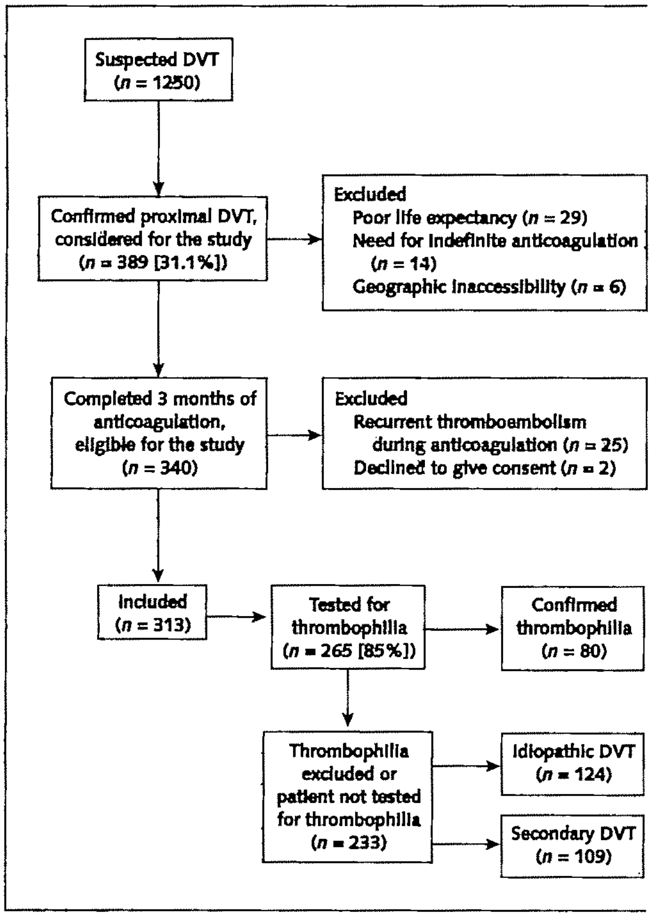
The first 3 months of initial anticoagulant treatment were not included in any of our analyses. For the remaining months, Kaplan–Meier estimates and 95% CIs were calculated to assess the risk for recurrent venous thromboembolism. Time-dependent multivariate Cox proportional hazards models were then used to calculate hazard ratios for recurrent venous thromboembolism in patients with residual thrombosis versus those without. For this analysis, patients who did not have a recurrence were censored at the end of the available follow-up or at death. In addition, the clinical categorization of patients was evaluated by using two dummy variables to indicate the presence of idiopathic DVT or thrombophilia. Secondary thrombosis was therefore used as the reference group, and in each case, the duration of oral anticoagulant treatment was used as a time-dependent covariate. Finally, all of these variables, as well as age and sex, were introduced in a stepwise hierarchical Cox model (16, 17). The results of these analyses were expressed as risk ratios and 95% CIs. In addition, incidence density of recurrent venous thromboembolism (events per observation-year) was calculated for the various combinations of clinical characteristics. All calculations were performed by using SAS software, version 6.10 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Patients

Of 1250 patients who were referred for clinical suspicion of first DVT, 389 (31.1%) received a diagnosis of proximal venous thrombosis on compression ultrasonography (Figure 1). Forty-nine of these 389 patients were excluded because of poor life expectancy ($n = 29$), diseases requiring permanent anticoagulation ($n = 14$), or inability to attend follow-up visits ($n = 6$). Of the remaining 340 eligible patients, 25 developed a recurrent thromboembolic event during initial anticoagulation. Therefore, 315 patients completed an uneventful 3-month period of anticoagulation. Of these, 313 agreed to participate and were enrolled in the study.

Figure 1. **Flow diagram for inclusion of patients in the study.**


Suspected DVT
(n = 1250)
Confirmed proximal DVT, considered for the study
(n = 389 [31.1%])
Excluded
Poor life expectancy (n = 29)
Need for indefinite anticoagulation (n = 14)
Geographic inaccessibility (n = 6)
Completed 3 months of anticoagulation, eligible for the study
(n = 340)
Excluded
Recurrent thromboembolism during anticoagulation (n = 25)
Declined to give consent (n = 2)
Included
(n = 313)
Tested for thrombophilia
(n = 265 [85%])
Confirmed thrombophilia
(n = 80)
Thrombophilia excluded or patient not tested for thrombophilia
(n = 233)
Idiopathic DVT
(n = 124)
Secondary DVT
(n = 109)

DVT = deep venous thrombosis.

Table 1. **Characteristics of the 313 Study Patients**

Variable	Value
Men, *n* (%)	146 (46.6)
Mean age ± SD, y	59.5 ± 17.6
Screened for thrombophilia, *n* (%)	265 (84.6)
Thrombophilia, *n*	80
Factor V gene mutation	34
Prothrombin gene mutation	19
Protein S deficiency	6
Protein C deficiency	4
Lupus-like anticoagulants	6
Antithrombin deficiency	5
Combination of two abnormalities	6
Idiopathic thrombosis, *n* (%)	124 (39.6)
Secondary thrombosis, *n* (%)	109 (34.8)
Duration of anticoagulation, *n* (%)	
3 mo	248 (79.2)
6–12 mo	65 (20.8)*

* In 19 of 80 patients with thrombophilia (23.7%), 26 of 124 patients with idiopathic thrombosis (21.0%), and 20 of 109 patients with secondary thrombosis (18.3%).

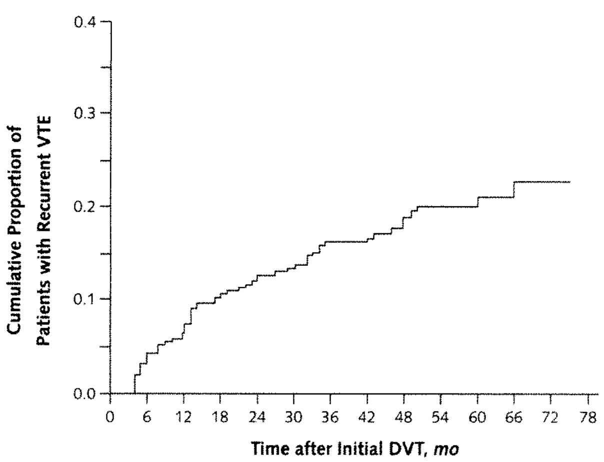
The main demographic and clinical characteristics of the study patients are presented in Table 1. Tests for thrombophilia were performed in 265 patients (85%), and 80 (30.2%) had positive results. One hundred nine patients had a thrombotic event associated with one or more triggering risk factors, and 124 had an idiopathic thrombotic event.

Although all patients had been instructed to stop anticoagulation after the initial 3-month period, 65 (20.8%) continued warfarin treatment for an additional 3 months ($n = 27$) or an additional 6 months ($n = 38$). Attending physicians decided to continue therapy on an individual basis, regardless of thrombophilia status or the results of ultrasonographic tests. As shown in Table 1, anticoagulation was continued for a few additional months in similar proportions of the three study groups (thrombophilic patients, patients with idiopathic thrombosis, and patients with thrombosis secondary to transient risk factors).

Cumulative Incidence of Normal Results on Ultrasonography

The first ultrasonographic assessment, performed 3 months after the initial event, yielded normal results in 61 patients (19.5%). The cumulative incidence of normal ultrasonographic results was 38.8% at 6 months, 58.1% at 12 months, 69.3% at 24 months, and 73.8% at 36 months. This rate did not differ significantly between patients with and those without thrombophilia (risk ratio,

Figure 2. **Cumulative incidence of recurrent venous thromboembolism (*VTE*), excluding events that occurred during the initial 3-month period.**



DVT = deep venous thrombosis.

0.91 [95% CI, 0.64 to 1.29]) or between patients with idiopathic thrombosis and those with secondary thrombosis (risk ratio, 0.89 [CI, 0.65 to 1.22]).

Recurrent Venous Thromboembolism

Of the 313 included patients, 110 presented during follow-up with clinically suspected recurrent venous thromboembolism; recurrent venous thromboembolism was confirmed in 58 (53%). In 44 patients, recurrences were thromboses involving a previously affected extremity (*n* = 19) or the contralateral leg (*n* = 25); the remaining 14 patients had pulmonary embolisms. Forty-one patients who experienced recurrences developed them while residual thrombosis was present. The cumulative incidence of recurrent thromboembolism was 4.2% of 296 patients at 6 months, 7.4% of 280 patients at 12 months, 12.7% of 258 patients at 24 months, 16.2% of 199 patients at 36 months, and 21.1% of 71 patients at 5 years (**Figure 2**). None of the 65 patients who continued warfarin treatment beyond the first 3 months developed thromboembolic recurrences while receiving anticoagulation.

Of the 58 patients who had recurrent events, 29 were in the thrombophilia group (29 of 80 patients [36.2%]), 20 were in the idiopathic DVT group (20 of 124 patients [16.1%]), and 9 were in the secondary thrombosis group (9 of 109 patients [8.3%]). Based on the Cox proportional hazards model, the hazard ratio for recurrent venous thromboembolism was 2.8 (CI, 1.5 to 5.0; $P = 0.001$) in patients with idiopathic thrombosis and 3.3 (CI, 2.0 to 5.5; $P = 0.001$) in patients with thrombophilia compared with patients who had secondary thrombosis.

Of the 58 recurrent episodes, 41 occurred while patients had residual thrombosis and 17 occurred after normalization of the affected veins. Using a time-dependent univariate Cox proportional hazards model, we found that the hazard ratio for a recurrent event was 2.9 (CI, 1.6 to 5.2; $P = 0.001$) when residual thrombosis was present. In a multivariate stepwise Cox proportional hazards model in which persistent residual thrombosis was used as a time-dependent variable, we determined that the hazard ratio for a recurrent event was 2.4 (CI, 1.3 to 4.4; $P = 0.004$) in patients with residual thrombosis, 2.5 (CI, 1.4 to 4.4; $P = 0.003$) in patients with idiopathic thrombosis, and 3.1 (CI, 1.8 to 5.2; $P < 0.001$) in patients with thrombophilia versus patients with secondary thrombosis. Age and sex did not appear in the final model. **Table 2** shows the related annual incidence density of recurrent venous thromboembolism in relation to type of initial thrombosis, presence of thrombophilia, recanalization of the thrombosed vein, and time elapsed since initial event.

DISCUSSION

In the past, patients with a first episode of DVT were usually treated for a fixed period of 3 months regardless of the underlying cause (18). Currently, there is a trend toward adjusting the duration of anticoagulation according to patients' clinical characteristics at baseline. Selected patients with permanent risk factors, such as active cancer, prolonged immobilization due to chronic medical illnesses, the antiphospholipid antibody syndrome, and other thrombophilic conditions, generally receive long (and sometimes lifelong) courses of oral anticoagulant therapy (1, 2, 19). In most patients without permanent risk factors, anticoagulation is usually withdrawn after a shorter period, ranging from 6 months to 2 years in patients with idiopathic thrombosis (4, 6, 7, 19, 20) and from 6 to 12 weeks in those with transient risk factors (4, 19, 20). However, in all patients, the risk for recurrence after a short, fixed period of anticoagulation varies greatly. Approximately 70%

Table 2. **Incidence Density of Recurrent Venous Thromboembolism***

Variable	Recurrent Venous Thromboembolism	
	3–24 Months since First DVT	**≥24 Months since First DVT**
Patients with thrombophilia		
Normal results on ultrasonography, %	10.3 (3.3–24)	7.1 (2.8–14.5)
Events per observation-years, *n/n*	5/48.5	7/99.1
Residual venous thrombosis, %	23.2 (13.3–37.7)	2.6 (0.1–14.5)
Events per observation years, *n/n*	16/68.9	1/38.3
Patients with secondary DVT		
Normal results on ultrasonography, %	0.0 (0.0–3.9)	0.0 (0.0–3.0)
Events per observation years, *n/n*	0/94.1	0/121.5
Residual venous thrombosis, %	7.1 (2.6–15.5)	4.9 (1.0–4.4)
Events per observation years, *n/n*	6/84.2	3/60.8
Patients with idiopathic DVT		
Normal results on ultrasonography, %	4.4 (1.2–11.2)	0.6 (0.0–3.4)
Events per observation years, *n/n*	4/91.4	1/166.2
Residual venous thrombosis, %	7.5 (3.2–14.7)	10.1 (4.1–20.9)
Events per observation years, *n/n*	8/107.3	7/69.0

* Values in parentheses are 95% CIs. DVT = deep venous thrombosis.

of patients with unexplained thrombosis do not develop a recurrence (3–7, 20), and 10% of patients with transient risk factors do (3–5, 20). Therefore, improving our ability to identify patients who are more likely to develop a recurrence might help clinicians individually tailor the duration of anticoagulation. This, in turn, would allow a more favorable risk–benefit ratio in the use of anticoagulant treatment.

Our results confirm that the lack of an identifiable cause and the presence of thrombophilic conditions in patients with a first episode of symptomatic DVT are both associated with increased risk for recurrent venous thromboembolism (3–7, 20–27). Our results also strongly suggest that the risk for recurrence is considerably higher in patients with residual venous thrombosis on repeated ultrasonography than in patients with early vein recanalization (hazard ratio, 2.4 [CI, 1.3 to 4.4]). Therefore, persistent residual venous thrombosis should be considered a powerful and independent risk factor for recurrent thromboembolism. In this respect, ultrasonographic testing performed at fixed intervals to monitor for thrombus evolution may help clinicians individually modify the duration of anticoagulant therapy, especially in persons with idiopathic DVT and those with transient risk factors for thrombosis.

On the basis of patient characteristics alone, risk estimates for recurrence in the first 2 years after an acute episode of DVT ranged from 4% per year (in patients with secondary thrombosis) to 15% per year (in patients with thrombophilia). Ultrasonographic testing widened this range from 0% (in patients with secondary DVT who had vein recanalization) to 23% (in patients with thrombophilia and residual vein thrombosis). In patients with idiopathic thrombosis and normal results on ultrasonography, the risk for recurrence (4% per year) was low enough to allow consideration of interrupting anticoagulation. Conversely, the incidence of recurrence in patients with secondary thrombosis and residual venous thrombosis, more than 7% per year, might indicate continuation of anticoagulant treatment. Of interest, persistent residual thrombosis was associated with an increased risk for recurrence in patients with thrombophilia. However, this finding was observed only in the first 2 years of our study, when the recurrence rate in patients with normal results on ultrasonography (10%) was also high enough to justify continued treatment.

The concept of adjusting the duration of therapy for acute DVT on the basis of normal ultrasonographic results is appealing. However, the only available study exploring early interruption of anticoagulation (after 4 weeks) in patients with normal results on impedance plethysmography found a disappointingly high risk for recurrence (28). It should be noted, however, that impedance plethysmography can yield normal results in patients with DVT even in the presence of extensive residual venous thrombosis. For example, results of impedance plethysmography are normal at 3 months in 90% of patients after acute proximal DVT (29, 30), while results of ultrasonography are normal in only 25%, as shown in this and in other investigations (12, 31). Moreover, 4 weeks of anticoagulant treatment is not considered sufficient according to current standards and might have contributed to the high recurrence rate (19). Our results, which are consistent with those of Piovella and colleagues (32), suggest that ultrasonography, unlike impedance plethysmography, can accurately quantify the persistence of residual thrombosis in proximal venous segments, thus enabling better stratification of recurrence risk.

What potential underlying mechanism leads to the relationship between persistent residual thrombosis and increased risk for recurrent thrombosis? Residual thrombosis could impair venous outflow, resulting in blood stasis with consequent clot formation. However, this seems unlikely. One third of our patients developed recurrent thrombosis in the initially unaffected leg, and an additional third developed isolated pulmonary embolism. Therefore, residual thrombosis probably reflects an underlying hypercoagulable state that puts patients at higher risk for recurrent events.

We believe our results are widely generalizable. Consecutive patients with clinically suspected and objectively confirmed DVT were prospectively followed for up to 6 years. All suspected recurrent events were objectively confirmed. The ultrasonographic method used to evaluate vein recanalization was based on findings obtained in a separate cohort of patients with proximal DVT. This method is highly reproducible, fast, and easy to perform because it involves examining only the midpopliteal and inguinal regions with a real-time B-mode scanner (12).

Our results suggest that patients with proximal venous thrombosis whose veins do not recanalize are likely to develop recurrent thrombotic events after withdrawal of oral anticoagulant therapy. These conclusions apply to patients with idiopathic venous thrombosis, patients with thrombosis secondary to transient risk factors, and patients with thrombophilic abnormalities. Assessment of the thrombotic burden, therefore, allows new opportunities for individual management of patients with venous thrombosis rather than management based on broad guidelines alone (33). In the future, randomized studies should assess the risks and benefits of adjusting the duration of oral anticoagulant therapy according to the presence or absence of residual venous thrombosis.

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BRIEF COMMUNICATION

Prevalence of Liver Disease in a Population of Asymptomatic Persons with Hepatitis C Virus Infection

Alfredo Alberti, MD; Franco Noventa, MD; Luisa Benvegnù, MD; Silvia Boccato, MD; and Angelo Gatta, MD

Background: **The prevalence of significant liver disease in persons with asymptomatic hepatitis C virus (HCV) infection is unclear.**

Objective: **To determine the prevalence and severity of HCV infection in asymptomatic persons.**

Design: **Population-based cross-sectional study.**

Setting: **Northeastern Italy.**

Patients: **4820 apparently healthy Telecom Italy employees or their relatives who underwent screening for cardiovascular risk factors.**

Measurements: **Initial screening for anti-HCV by enzyme-linked immunosorbent assay followed by HCV RNA testing by polymerase chain reaction and monitoring of alanine aminotransferase levels in viremic persons (92% of viremic persons also had liver biopsies to assess their METAVIR scores).**

Results: **116 persons (2.4% [95% CI, 1.97% to 2.84%]) were positive for anti-HCV and 85 (1.76% [CI, 1.39% to 2.14%]) were also viremic. The ALT level was persistently normal in 39 (46%) of viremic patients and elevated in 46 (54%). Significant hepatic histologic abnormalities were detected in 19% (CI, 7.21% to 36.4%) of persons with persistently normal ALT levels and in 61% (CI, 45.4% to 74.9%) of viremic persons who had elevated ALT levels ($P < 0.001$). The prevalence of HCV infection and number of persons with chronic liver fibrosis increased with age ($P = 0.003$).**

Conclusions: **Hepatitis C is histologically active and progressive in up to 40% of asymptomatic persons with HCV infection. The severity of liver disease correlates with abnormal ALT levels and increases with age.**

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Although new hepatitis C virus (HCV) infections have declined during the past decade in most developed countries (1), hepatitis C remains a major health problem because of the many persons infected before serologic testing became available (2, 3). Many persons with HCV infection are asymptomatic and unaware that they are infected. While it is clear that HCV contributes greatly to end-stage liver disease, the natural history of hepatitis C in asymptomatic individuals is poorly defined.

Published studies indicate that the natural history of hepatitis C is heterogeneous. Several factors, including age at infection, alcohol use, and co-infection with hepatitis B virus or HIV, increase the risk for cirrhosis (4–8). Independent of these cofactors, prognosis is related to hepatic histopathology, particularly the type and amount of liver necroinflammation and fibrosis (9–11). Our understanding of the histology of hepatitis C in asymptomatic persons comes mainly from studies of blood donors (a selected population) (12–14). We report an investigation of the prevalence, histologic activity, and stage of HCV infection in 4820 otherwise apparently healthy adults living in northeastern Italy.

METHODS

Patients

We tested for serum anti-HCV in 4820 adults (2132 men and 2688 women; age range, 16 to 60 years) who were undergoing a screening program for cardiovascular risk factors. To be eligible for this program, persons had to be free of acute or chronic illness (based on history and clinical symptoms) at the time of evaluation. Telecom Italy proposed and promoted the screening program to employees and their relatives. Participation was voluntary. Participants lived in one of three regions (Veneto, Trentino-Alto-Adige, and Friuli-Venezia-Giulia) in northeastern Italy and included a wide range of socioeconomic strata (from employees in lower positions to senior managers and their relatives).

All 4820 persons (1210 employees and 3610 relatives) gave written informed consent and underwent clinical evaluation and testing for anti-HCV by enzyme-linked immunosorbent assay (ELISA) (Ortho Diagnostic Systems, Raritan, New Jersey) at the initial visit. Within 1 month, we retested persons who were positive for anti-HCV by ELISA. Serum that was confirmed to be HCV positive was tested for HCV RNA by polymerase chain reaction (PCR) (Amplicor HCV Monitor test, Roche Diagnostics, Indianapolis, Indiana). We retested serum for HCV RNA after 1 and 3 months in confirmed anti-HCV–positive persons whose initial test results for HCV RNA had been negative. We monitored serum alanine aminotransferase (ALT) levels 1, 3, 6, and 12 months after anti-HCV detection. We proposed liver biopsy for all viremic persons. These biopsies were done 6 to 14 months after detection of anti-HCV; patients provided informed consent. Liver biopsy specimens were evaluated according to the METAVIR scoring system (15). We classified patients with METAVIR scores of F2 and higher or A2 and higher as having "significant" liver disease according to international guidelines (16).

Statistical Analysis

Prevalences of HCV infection and of liver disease were compared by using the Fisher exact test for 2 × 2 tables.

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Context

Many persons infected with hepatitis C virus (HCV) are asymptomatic. The extent of liver disease in these persons is unclear.

Contribution

The researchers tested 4820 apparently healthy persons in Italy for hepatitis C virus. Among the 116 (2.4%) who tested positive, 85 were viremic; only about half of these 85 patients had elevated alanine aminotransferase (ALT) levels. Liver biopsy showed substantial inflammation or fibrosis in 19% of persons with normal ALT levels and 61% of persons with abnormal ALT levels.

Implications

The substantial prevalence of abnormal liver histology among asymptomatic persons is a provocative but incomplete rationale for screening for HCV. The prevalence of infection and the effectiveness of treatment are also important considerations.

—The Editors

The chi-square test for linear trend was used to compare prevalences in age subgroups.

Role of the Funding Source

The study protocol was developed by a Scientific Committee of the Italian National Research Council (CNR), approved by a National Ethical Committee, and directly funded by the Italian National Research Council. The Italian National Research Council had no role in the collection, analysis, and reporting of the study or in the decision to publish the manuscript.

RESULTS

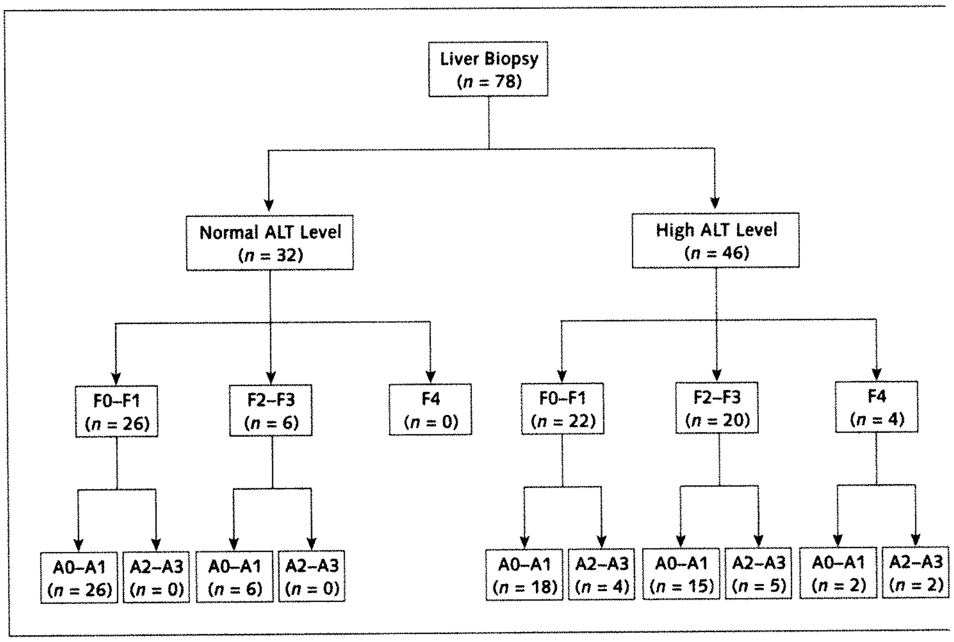
Prevalence of HCV Infection in the Screened Population

Of the 4820 persons tested, 116 (2.4% [CI, 1.97% to 2.84%]) were repeatedly positive for anti-HCV by ELISA and 12 additional persons were initially positive but were negative on repeated testing. Samples confirmed to be anti-HCV positive were tested for HCV RNA; 75 of these were positive. The 41 persons who were initially positive for anti-HCV but negative for HCV RNA were tested for serum HCV RNA 1 and 3 months after anti-HCV detection; 10 were positive in both (*n* = 8) or one (*n* = 2) follow-up test. Thus, 85 of 116 anti-HCV–positive persons (73.3%), or 85 of 4820 screened individuals (1.76 % [CI, 1.39% to 2.14%]) were positive for HCV RNA. Among the 85 HCV RNA–positive individuals, ALT levels were normal (<50 U/L) at all times (at 0, 1, 3, 6, and 12 months) in 39 persons (46%), elevated at all times in 37 persons (43.5%), and abnormal at least once in 9 patients (10.5%). The 10 persons with intermittent HCV RNA positivity had persistently normal ALT levels during follow-up.

Liver Histology in HCV-Infected Persons

Seventy-eight of the 85 persons who were positive for HCV RNA had liver biopsies; these 78 patients included 32 of 39 persons with persistently normal ALT levels and all 46 persons with elevated ALT levels. The **Figure** summarizes the histopathologic characteristics of the 78 HCV-

Figure. **Histologic activity and fibrosis stage of the 78 persons with normal or elevated alanine aminotransferase levels who were positive for hepatitis C virus.**



A = necroinflammatory activity; ALT = alanine aminotransferase; F = fibrosis score.

Table. **Liver Histology during the 12-Month Follow-up Period in 78 Hepatitis C Virus–Positive Persons***

Liver Histology	Mean ALT Value			Peak ALT Value		
	<50 U/L (Normal) (*n* = 35)	50–75 U/L (*n* = 28)	>75 U/L (*n* = 15)	<50 U/L (Normal) (*n* = 32)	50–100 U/L (*n* = 27)	>100 U/L (*n* = 19)
	←			*n* (%)		→
Necroinflammatory activity						
A0–A1	35 (100)	23 (82)	9 (60)	32 (100)	23 (85)	12 (63.2)
A2–A3	–	5 (8)	6 (40)	–	4 (15)	7 (36.8)
Fibrosis score						
F0	10 (28.6)	–	–	9 (28.1)	1 (3.7)	–
F1	18 (51.4)	13 (46.4)	7 (46.7)	17 (53.1)	13 (48.1)	8 (42.4)
F2	6 (17.1)	8 (28.6)	3 (20)	5 (15.6)	8 (29.6)	4 (24.1)
F3	1 (2.9)	5 (17.9)	3 (20)	1 (3.2)	3 (44.4)	5 (26.3)
F4	–	2 (7.1)	2 (13.3)	–	2 (2.5)	2 (10.5)

* Values are the number (percentage) of patients. ALT = alanine aminotransferase.

positive persons according to the ALT profile during the observation period. Overall, 52% of patients with elevated ALT levels and 19% of patients with normal ALT levels had significant fibrosis (F2 to F4), whereas 24% of patients with elevated ALT levels and none with normal ALT levels had significant necroinflammatory activity (A2 to A3). Thus, on the basis of a fibrosis score of 2 or higher or an activity score of 2 or higher, moderate to severe chronic hepatitis was seen in 28 of 46 (61% [CI, 45.4% to 74.9%]) patients with elevated ALT levels and in 6 of 32 (19% [CI, 7.21% to 36.4%]) patients with normal ALT levels ($P < 0.001$). Both mean and peak ALT values during the 12-month follow-up period correlated with activity and fibrosis stage (Table). The percentage of patients with significant activity or fibrosis increased with increasing ALT levels (data not shown).

Prevalence of HCV Infection and Liver Disease by Age

Prevalence of HCV RNA positivity increased with age: 0.67% (CI, 0.23% to 1.57%) in persons age 16 to 30 years, 1.4% (CI, 0.93% to 2.08%) in persons age 31 to 45 years, and 2.4% (CI, 1.8% to 3.2%) in persons age 46 to 60 years ($P = 0.003$). The percentage of persons with persistently normal ALT levels was similar in the three age groups, but severity of liver disease increased with age. The prevalence of significant fibrosis (≥F2) was 20% in the persons age 16 to 30 years and 48% in the persons age 46 to 60 years. When only patients with abnormal ALT levels were considered, the corresponding figures were 33% in persons age 16 to 30 years, 50% in the persons age 31 to 45 years, and 79% in the persons age 46 to 60 years.

HCV Genotypes

Among the 85 persons positive for HCV RNA, 52 (61.2%) were infected with HCV genotype 1b, 5 (5.8%) with genotype 1a, 20 (23.5%) with genotype 2a/2c, and 8 (9.4%) with genotype 3. Four of 5 patients age 16 to 30 years were infected with genotype 3, and the fifth was infected with genotype 1a. Genotype in persons age 31 to 45 years and 46 to 60 years did not differ significantly. The HCV genotypes were not significantly associated with ALT levels or histologic features after adjustment for age (dat not shown).

DISCUSSION

It has been difficult to estimate precisely how man asymptomatic HCV-infected persons are at significant ris for progressive liver disease. This is a result of the limite available information on the actual burden of HCV in th general population and uncertainty about the natura course of HCV infection in asymptomatic individuals (16) Previous studies mainly considered blood donors screene for anti-HCV and rarely reported systematic data on live histology. Our survey was conducted in a less highly selected population and might therefore better represent th burden of HCV in the general population.

Limitations of our study include the uncertain generalizability to other geographic areas, the inclusion of onl working adults and their relatives, and the lack of detaile information on risk factors in the screened population an of cofactors known to influence hepatitis C progressio (use of alcohol or drugs; co-infection with hepatitis B viru or HIV) in the HCV-positive persons. Our data may underestimate the prevalence of HCV because of a health worker effect.

Despite these limitations, our data indicate that progressive liver disease can be detected in a substantial proportion of apparently healthy, asymptomatic persons wit HCV infection. Of note, almost 40% of individuals positive for HCV RNA, representing 0.70% of the genera population cohort screened, had active inflammatory lesions or advanced fibrosis (as shown by liver biopsy results). These histologic features are considered the hallmar of progressive HCV infection and indications for antivira therapies (16). Our findings would suggest that broade screening for HCV in the general population might b indicated in geographic areas with intermediate to hig prevalences of HCV infection. Initiation of wider screening may be optimal now because current treatment of hepatitis C with the combination of pegylated interferons an ribavirin leads to a sustained virologic response greater than 50% (17).

Previous studies reported less severe histologic lesions in HCV carriers with normal ALT levels (18, 19). This was also true in our patients. However, as previously described (20), significant fibrosis was also seen in patients with normal liver enzyme levels, and this observation might have implications for performing liver biopsies in HCV-positive persons with normal ALT levels.

We observed a clear relationship between age and severity of liver disease. Although the number of asymptomatic persons with HCV and normal ALT levels was consistent among age subgroups, increasing age was associated with a progressive reduction in the number of persons with mild disease and a corresponding increase in severe hepatitis and cirrhosis. This may reflect a more progressive course of HCV infection in older patients. Another possibility is that it may indicate that the disease is mild and does not progress in about half of the patients (mainly those with normal ALT levels) and progresses slowly but consistently in the other half. We compared our data on the natural course of hepatitis C with those described in published series of clinically recognized cases of chronic hepatitis (4, 5, 8). Our data on mild and on progressive disease in different age subgroups are compatible with the approximate 20% progression rate from initial to intermediate fibrosis and 20% progression rate from intermediate fibrosis to cirrhosis over a 10- to 15-year period.

In conclusion, our study demonstrates that the spectrum of liver disease in asymptomatic and newly diagnosed HCV-positive persons is broad. A substantial proportion of asymptomatic persons with HCV infection have disease that is histologically active enough to warrant antiviral therapy.

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COMPLEMENTARY AND ALTERNATIVE MEDICINE SERIES
Series Editors: David M. Eisenberg, MD, and Ted J. Kaptchuk, OMD

Credentialing Complementary and Alternative Medical Providers

David M. Eisenberg, MD; Michael H. Cohen, JD; Andrea Hrbek; Jonathan Grayzel, MD; Maria I. Van Rompay, BA; and Richard A. Cooper, MD

Since the late 19th century, state legislatures and professional medical organizations have developed mechanisms to license physicians and other conventional nonphysician providers, establish standards of practice, and protect health care consumers by establishing standardized credentials as markers of competence. The popularity of complementary and alternative medical (CAM) therapies presents new challenges. This article describes the current status of, and central issues in, efforts to create models for health care credentialing of chiropractors, acupuncturists, naturopaths, massage therapists, and other CAM practitioners. It also suggests a strategy of CAM provider credentialing for use by physicians, health care administrators, insurance companies, and national professional organizations.

The credentialing debate reflects fundamental questions about who determines which providers and therapies will be accepted as safe, effective, appropriate, and reimbursable. More nationally uniform credentialing mechanisms are necessary to ensure high standards of care and more generalizable clinical research. However, the result of more uniform licensure and credentialing may be excessive standardization and a decrease in individualization of services. Thus, increased standardization of credentialing for CAM practitioners may alter CAM practice substantially. Furthermore, even credentialed providers can deliver ineffective therapy. The suggested framework balances the desire to protect the public from dangerous practices against the wish to grant patients access to reasonably safe and effective therapies.

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Since the late 19th century, state legislatures and professional medical organizations have developed mechanisms to license physicians and other conventional nonphysician providers, establish standards of practice, and protect health care consumers by establishing standardized credentials as markers of competence. The recent explosion in the popularity of complementary and alternative medical (CAM) therapies (for example, chiropractic, acupuncture, naturopathy, massage therapy, homeopathy, and herbal medicine) presents new questions. Legislative recognition trumps medical recognition: State legislatures can license providers and thereby grant citizens access to certain therapies, even if scientific debate has not concluded in favor of those modalities. We describe the central issues in credentialing CAM providers and provide a framework for use by physicians, health care administrators, insurance companies, and national professional organizations.

CURRENT CREDENTIALING PRACTICES

Licensing and Credentialing of Medical Doctors, Doctors of Osteopathy, Registered Nurses, and Other Conventional Health Care Professionals

Credentialing is "the process of obtaining, verifying, and assessing the qualifications of a health care practitioner to provide patient care services in or for a health care organization" (1). Such qualifications may include a state license (granting the right to practice), which includes, in the case of providers other than medical doctors, a legislatively designated scope of practice (that is, the right to offer a specified range of clinical services that is narrower than medical diagnosis and treatment). Clinical "privileges," also known as medical staff privileges, are the authorization granted by the appropriate authority (for example, a governing body) to a practitioner to provide specific care services in a health care organization or network within well-defined limits (2). Thus, credentialing a provider to deliver clinical services does not necessarily make the provider a member of the medical staff with clinical "privileges."

Licensure requirements for medical doctors and doctors of osteopathy include graduation from a Liaison Committee on Medical Education (LCME)–accredited school or the equivalent, a passing grade on all three parts of the United States Medical Licensing Examination, and a minimum of 1 year postgraduate training in an accredited program (**Appendix** Table 1, available at www.annals.org). Requirements for nursing licensure include graduation from an accredited nursing program and a passing grade on the National Council Licensure Examination (NCLEX) (3). Licensing requirements and scope of practice for other conventional health care providers, such as physical therapists, optometrists, and podiatrists, vary by profession and by state (**Appendix** Table 2, available at www.annals.org) (4).

Licensing and Credentialing of CAM Providers

Licensing of CAM practitioners also varies by type of practitioner and by state (**Appendix** Table 3, available at www.annals.org). For example, chiropractic is licensed in every state, whereas massage therapy is licensed in some states but not others and is less amenable to a national credentialing process. Some practices (for example, homeopathy) by and large lack formal recognition through state licensure and, therefore, afford hospitals and health plans no coherent credentialing process (5) (**Table 1**). Moreover, the type of license granted to each kind of provider varies by state (that is, mandatory license, title license, or registration) (6). Finally, as with conventional nonphysician providers, legal recognition of CAM providers through licensure is a political process, with attendant debates over scope of practice, prescriptive authority, and role of physician supervision (4).

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Table 1. **Overview of Licensing Requirements for Complementary and Alternative Medical Practitioners***

Profession	States with Licensure, *n*	Education	
		Training	Internship/Residency
Chiropractors (DC)	50 and District of Columbia	4–5 years or 4200 hours; includes basic medical sciences as well as clinical experiences	None
Non-MD acupuncturists	42 and District of Columbia	3 years or 1800 hours; includes 300 hours Chinese herbology and 500 clinical hours; some states require anatomy, physiology, and pathology, but 17 have no specific requirement	None
MD acupuncturists	31 states expressly include acupuncture in MD and DO licensure; 11 states require additional training or an examination; 4 states do not have any ruling; 2 states do not permit	200–300 hours	None
Naturopathic doctors (ND)	11	4-year postgraduate program; years 1 and 2 emphasize natural sciences; years 3 and 4 emphasize the clinical sciences and a range of natural therapeutics	None required; however, graduates are increasingly participating in residency training programs
Massage therapists	25	100–1000 hours; most states specify a minimum of 500 hours; states may specify graduation from a Commission on Massage Therapy Accreditation (COMTA)–approved program, an equivalent program, or training in a specific area (e.g., anatomy or theory)	None
Homeopathic physicians†	3; Licensure as a homeopathic physician is available only to MDs and DOs in Nevada, Arizona, and Connecticut	Nevada specifies 6 months of postgraduate training; Arizona requires 300 hours of postgraduate training; Connecticut does not specify any educational requirements	NA

* Verified as of July 2001. CE = continuing education; CEU = continuing education unit; DO = doctor of osteopathy; NA = not applicable.
† Other practitioners, such as naturopathic doctors, may be trained in and include homeopathy in their legislative scope of practice; however, only MDs are currently eligible for licensure.

Chiropractic

Chiropractic, first licensed in 1904 by Illinois, is now licensed in all states. Currently, approximately 70 000 licensed chiropractors are practicing in the United States (**Figure 1** and **Appendix Table 4**, available at www.annals.org) (7). Students train at 1 of 16 chiropractic colleges accredited by the Council on Chiropractic Education, an organization recognized by the U.S. Department of Education (DOE) (7, 8). The Federation of Chiropractic Licensing Boards has developed uniform standards of education and examination, including the National Board of Chiropractic Examiners' four-part standard national certification examination; parts 1 to 3 are required for licensing by almost all states (**Table 1**) (9, 10).

However, obstacles to standardized credentialing persist, including understanding the scope of practice variations across states for chiropractors (6). For example, states vary in authorizing chiropractors to dispense or sell dietary supplements or to use ancillary CAM therapies, such as homeopathy and acupuncture (7). Indeed, current debates surrounding the safety and efficacy of dietary supplements highlight dilemmas involved in regulating providers' authority to recommend or offer such supplements (11, 12).

Yet another conundrum is the status of chiropractors as "primary care providers" (PCPs). The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) defines a primary care provider as an individual "who provides primary care services" (that is, "basic health care") and "manages routine health care needs," including "referral to a specialist for consultation or continued care" (13). The American Chiropractic Association defines chiropractors as "a first-contact gatekeeper" for patients with neuromusculoskeletal conditions in the primary health care system (14), and, in smaller communities with fewer physicians, chiropractors frequently serve as providers of first contact (7). In Illinois, chiropractors who meet rigorous standards, including review by a credentialing committee composed of conventional physicians, can receive re-

Table 1—**Continued**

Examination		Continuing Education Units
Written	**Practical**	
All states and District of Columbia accept or require the National Board of Chiropractic Examiners (NBCE) examination	40 states accept or require the NBCE Part IV examination (Practical Examination of Clinical Skills)	48 states and District of Columbia require some CEUs; average is 12 hours per year
National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) or state examination required in all states except Louisiana	Some states require the Practical Examination of Point Location Skills (PEPLS) or state examination	16 states require at least some CEUs; average is 15 hours per year
Only Hawaii requires MD acupuncturists to pass the same examination as non-MD acupuncturists; other states require only documentation of training	Only Hawaii has the same requirements for MD and non-MD acupuncturists	None
Naturopathic Physicians Licensing Examination (NPLEX) includes a basic sciences examination (not required by 2 states) and clinical examinations in clinical, physical, and laboratory diagnosis; diagnostic imaging; botanical medicine; pharmacology; nutrition; physical medicine; homeopathy; minor surgery; psychology; lifestyle counseling; and emergency medicine	None	4 states have laws requiring CE, but only 2 have specific requirements
16 states require passage of the National Certification Examination for Therapeutic Massage and Bodywork (NCETMB); 7 states have their own examination	2 states	State requirements range from 3 to 12 hours per year
Each state administers its own oral or written examination		Only Nevada requires CEUs (20 hours/year)

imbursement under a Blue Cross/Blue Shield plan as PCPs (15). The "PCP" status of chiropractors thus remains controversial.

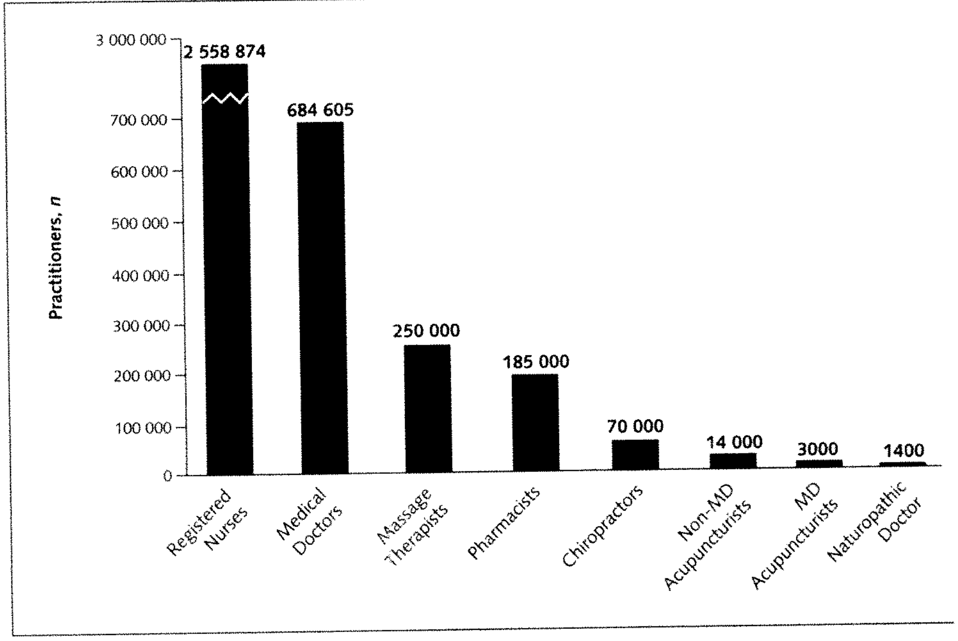
Acupuncture and Traditional Oriental Medicine

Acupuncture, first licensed by Nevada, Oregon, and Maryland in 1973, currently is licensed in 42 states and the District of Columbia (16). More than 14 000 practitioners are licensed in the United States (17), and an additional estimated 3000 medical doctors have studied formally and incorporate acupuncture into their practices (18). Of the more than 70 schools of acupuncture in the United States, 37 are accredited by and 9 are in candidacy status with the U.S. DOE–recognized Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) (**Figure** 2 and **Appendix** Table 4, available at www.annals.org).

About one third of the states that license nonphysician acupuncturists require graduation from an ACAOM school or one with an equivalent curriculum (17). In addition, approximately one third of licensing states require the study of biomedical sciences, including anatomy, physiology, and pathology (**Table** 1). The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) offers separate certification programs in Acupuncture, Chinese Herbology, and Oriental Bodywork Therapy (19). As with chiropractic, almost all states licensing acupuncturists require passage of a national written examination offered by NCCAOM (17). Twelve states also require passage of the NCCAOM practical examination (9, 17).

Credentialing problems persist. First, state requirements to practice acupuncture vary (**Table** 1 and **Appendix** Table 5, available at www.annals.org). In many states, acupuncture training requirements for medical doctors, dentists, and other allopathic providers are minimal or nonexistent (**Table** 1) (17, 20). Some states permit licensed CAM providers, such as chiropractors, to practice acupuncture (with varying levels of training) whereas other states prohibit it (17).

Figure 1. **Complementary and alternative medical and conventional practitioners.**



Second, states vary in their defined scope of practice for acupuncture and Oriental medicine. Definitions may include, in addition to needling, the following: magnets, laser biostimulation, cupping, Oriental bodywork (such as Shiatsu or acupressure), dietary counseling, reflexology, and other treatments (17). Some states specifically permit use of Chinese herbal medicine or western dietary advice and nutritional supplements; at least one state (Illinois) specifically prohibits use of herbal preparations (17). Colorado specifically prohibits use of western medical diagnostic tests and procedures; New Mexico's Board of Oriental Medicine authorizes doctors of Oriental medicine to order computed tomography, magnetic resonance imaging, and radiographs (17). Four states (Arkansas, Illinois, Utah, and Virginia) expressly prohibit spinal manipulation or chiropractic techniques (17).

Third, only 14 states have an independent board of acupuncture or Oriental medicine; in other states, acupuncturists are under the board of medical examiners or regulated by the departments of commerce or health (17, 21). Fourth, only two states (Florida and New Mexico) specify that acupuncturists provide primary care (22, 23). Approximately one quarter of the states licensing acupuncturists require prior referral from, diagnosis by, or collaboration with a licensed medical doctor (**Appendix Table** 5, available at www.annals.org) (17, 21).

Finally, ongoing intraprofessional disputes include educational prerequisites for licensure; use of the title "doctor" (of acupuncture or Oriental medicine); supervision, referral, and prior diagnosis requirements; and educational requirements for inclusion of Chinese herbology within scope of practice (21).

Naturopathy

Naturopathy, although practiced in the United States for more than a century, is licensed by only 11 states (**Table 1**). The 1400 licensed naturopaths in the United States (8) have trained at one of four naturopathic colleges accredited by the Council on Naturopathic Medical Education of the American Association of Naturopathic Physicians (AANP) (**Figure 2**). Although the AANP has developed a national certification examination, the Naturopathic Physicians Licensing Examination (NPLEX), passing is not required for licensure in all states. (**Table 1**) (9, 24–27).

As with chiropractic and acupuncture, the scope of practice for naturopathy varies widely by state. For example, naturopaths with appropriate specialty training can assist in childbirth in Montana, New Hampshire, Oregon, and Utah (28–31); in some states, they can practice acupuncture (17).

Intraprofessional disputes include objections to licensure requirements by individuals who use the title of naturopath but who have little (or no) training, particularly in states lacking naturopathic licensure, and whether to actively recommend standard immunization procedures (32). Although naturopaths are not required to obtain postgraduate (that is, residency) training or supervision, they are described as primary caregivers in some of their licensing statutes (6) and are seen as health care providers of first contact by many patients.

Massage Therapy

The number of massage therapists has increased from approximately 75 000 in 1995 to more than 250 000 in 2002 (33). The American Massage Therapy Association

(AMTA), a nonprofit professional organization, founded two regulatory boards: the Commission on Massage Therapy Accreditation (COMTA), which accredits massage therapy schools, and the National Certification Board for Therapeutic Massage and Bodywork (NCBTMB), which certifies practitioners on successful completion of a national examination. Increasingly, states are requiring as a basis for licensure that massage therapists 1) have a minimum of 500 hours of in-class, supervised training at an accredited institution; 2) have passed the NCBTMB national certification examination, 3) maintain specified continuing education requirements, and 4) carry minimum malpractice insurance (Table 1).

Numerous other professional organizations in addition to the AMTA represent providers; these include the Association of Bodywork and Massage Professionals (ABMP) and smaller, more specialized organizations, such as the American Organization for Bodywork Therapies of Asia (AOBTA) and Feldenkrais Guild of North America (FGNA). Approximately half of massage therapy practitioners do not belong to any professional organization (34). Although numerous accrediting organizations exist, only COMTA's accrediting process includes programmatic evaluation, and COMTA has accredited only 42 of approximately 1000 massage therapy schools in the United States (Figure 2).

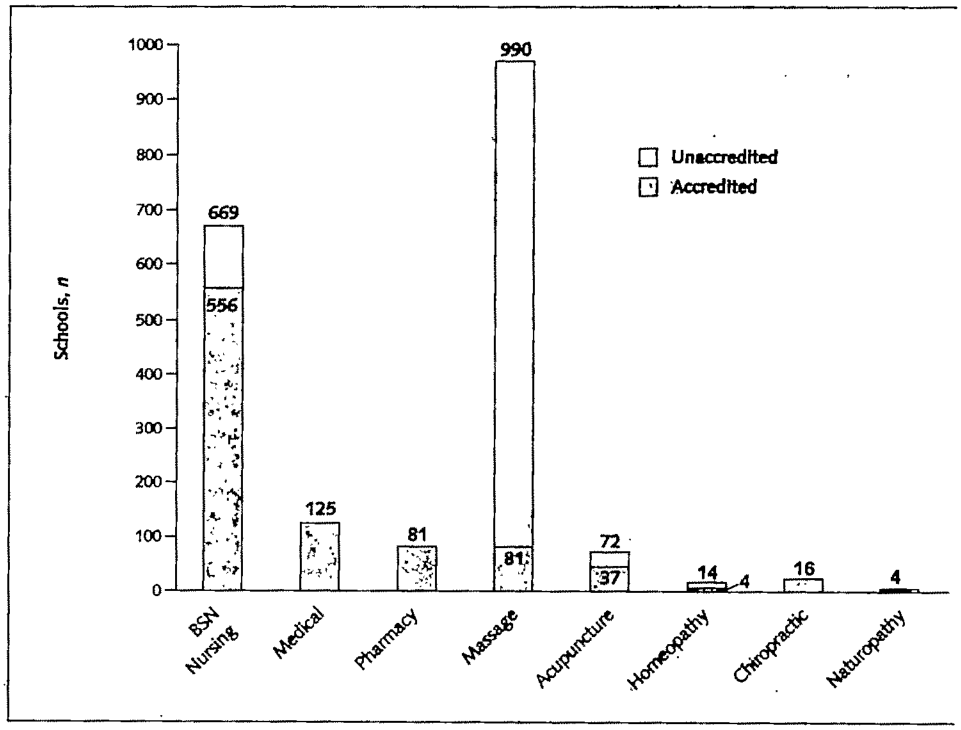
Many states (for example, California and Massachusetts) do not license massage therapists. Debate also arises as to whether licensing should be mandatory, required to claim a title such as "massage therapist," or whether therapists should only be required to register with a state agency. In Maryland, for example, practitioners are distinguished as registered massage practitioners or certified massage therapists on the basis of education (**Appendix Table 6**, available at www.annals.org); in other states, regulation is by town ordinance.

Scope-of-practice conflicts can also arise between massage therapists and other practitioners, such as physical therapists and chiropractors (for example, conflict over the exclusivity of hydrotherapy, recommendations for exercise, and certain kinds of tissue manipulation). Finally, although many massage therapists use western medical systems of anatomy and pathology, others rely primarily on eastern medical traditions (such as Shiatsu, which is based on acupuncture meridians).

Homeopathy

Homeopathy is widely practiced in the United States by a variety of practitioners (estimated at 6000) (35); however, only three states (Arizona, Connecticut, and Nevada) license homeopaths and then only if practitioners have medical licensure. Arizona and Nevada also license homeopathic assistants who can perform medical services under the supervision of a homeopathic physician (36, 37). Some states expressly include homeopathy within the scope of practice of professions such as chiropractic, naturopathy, physical therapy, and veterinary medicine (6); many nurses

Figure 2. **Complementary and alternative medical and conventional schools.**



BSN = Bachelor of Science in Nursing.

Table 2. **Credentialing Framework***

Minimum Requirements (Source verification for all documents is recommended.)
- Copy of current license (including expiration date) from the state or presiding jurisdiction (e.g., municipality) when state licensure is not available
- Evidence of satisfactory completion of national certification examination (not required for licensure in all states); in the absence of state regulation, however, this represents a uniform standard for training and for a knowledge base
- Copy of diploma from an accredited professional school and evidence of college education if required
- Documentation of postgraduate studies (including certificates and diplomates) from an accredited school or program
- Evidence of continuing education units may be required for licensure or for membership in a professional organization
- Evidence of malpractice insurance in the form of an insurance binder; see Appendix Table 7 (available at www.annals.org) for recommended levels of coverage
- Review history of malpractice liability (including claims, judgments, and settlements); charges of misconduct; and disciplinary action by any federal, state, or local regulatory authority; can be obtained from a licensing board, professional organization, or malpractice insurance carrier

Optional and Additional Requirements
- Consider years in practice after establishing a minimum requirement; verification of work history is recommended
- Evaluate practice demographic characteristics (including office hours, location, practice type [private, multidisciplinary, or group], and patient volume) as well as office staffing, type of patient and percentage of population (e.g., workers' compensation, managed care, Medicare, Medicaid, third-party liability), and languages spoken by providers and staff
- Determine whether comprehensive general liability insurance is within satisfactory limits
- Review letters of recommendation from MDs, DOs, or peers with whom provider has comanaged patients
- Evaluate the provider's self-reported scope of practice; this should be compared with 1) level of training (to confirm training or certification for specific techniques or therapy) and 2) legislated or a specific scope of practice, such as the one developed for a clinical trial
- Conduct site visits that include evaluation of 1) location (handicap accessibility, parking, and public transportation) and 2) office environment, with categories and criteria clearly defined—office hours and availability, practice coverage, income from sales of products (e.g., dietary supplements) or services (e.g., radiography and blood tests)
- Reviews charts to document that specific elements consistently appear in patient/client records. These include history, examination, diagnosis, and a treatment plan
- Identify whether provider has full or limited/partial hospital privileges or other clinical affiliations

and dentists also incorporate homeopathy (38). Moreover, because most homeopathic remedies are classified as over-the-counter drugs (39), they are widely available.

The American Board of Homeotherapeutics provides board certification for licensed medical and osteopathic doctors after a written and oral examination, including presentation of clinical cases. Several boards offer certification for various nonlicensed and licensed health professionals, although these organizations lack recognition by the U.S. DOE. Major issues include the requisite level of training for competence in homeopathy, the different standards for training and certifying various providers (40), and legal status of lay practice of homeopathy (6, 38).

Other Complementary Care Providers

Licensed medical doctors generally have statutory authority to diagnose and treat disease. Thus, subject to medical board discipline for "unprofessional conduct" (6, 41, 42) or potential malpractice liability (43), medical doctors may incorporate CAM therapies. The more limited scope of practice allowed conventional nonphysician providers and licensed CAM practitioners; however, either permits or prohibits them from using specific CAM treatments (for example, nutritional counseling, herbal medicine, biofeedback, or hypnotherapy) or, more typically, fails to provide guidance (6, 44). Because scope of practice is complex and varies by state, guidance from legal counsel or relevant professional organizations may be helpful (43).

Providers who lack licensure share a complex and uncertain legal status. These providers include herbalists, lay homeopaths, unlicensed naturopaths, hypnotherapists, energy healers, mind–body practitioners, and others without any other health care licensure (44). Many of these providers have historically been prosecuted and convicted for the unlicensed practice of medicine (6, 45–51) or risk prosecution for unlicensed practice of another profession, such as massage therapy or psychology (6). Recently, Minnesota (52), California, and Rhode Island enacted legislation protecting such providers as long as they meet specific regulatory requirements, but physician referrals to both licensed and unlicensed CAM providers could, under some circumstances, increase potential malpractice liability (43).

A PROPOSED FRAMEWORK FOR CREDENTIALING CAM PROVIDERS

As we suggested earlier, the framework for physicians and other conventional health care providers offers a starting point for credentialing CAM providers. The following proposed framework draws on National Institutes of Health (NIH)–funded projects involving the identification of qualified CAM practitioners in the provision of chiropractic, acupuncture, and massage therapy for patients with acute or chronic low back pain. The minimum requirements include licensure; evidence of satisfactory completion of an appropriate national certification examination; documentation of completion of required studies and continuing education; and signed statements pertaining to malpractice insurance, history of malpractice, and disciplinary action (**Table 2** and **Appendix Table 7**, available at www.annals.org, for sample minimum standards for malpractice liability insurance). Credentials help assess competence but do not guarantee competence or that the therapist is using treatments proven to be safe or effective.

The optional requirements may help physicians or institutions seeking a higher level of quality assurance in selecting individual practitioners. These include minimum number of years in practice, demographic characteristics of the practice, and information about office staffing (**Table 2**). Furthermore, letters of recommendation from medical doctors, doctors of osteopathy, other conventional practitioners, and peers are useful to evaluate patient comanagement. Similarly, site visits can help evaluate the following: patient accessibility (for example, handicap access); office environment or written materials being distributed; the sale of products; the use of diagnostic or laboratory equipment (for example, radiography and blood tests); and appropriate medical record keeping (through random chart reviews). Inquiry into the provider's professional history may further help assess competence.

Finally, it is useful to identify therapeutic and diagnostic procedures most commonly used for each profession as a guideline to identify practitioners whose standard practice falls within the defined parameter for the clinic or research project. For example, in our ongoing NIH-funded studies, nationally representative groups of CAM professionals compiled broad lists of techniques commonly used by acupuncturists, chiropractors, and massage therapists to treat low back pain (**Appendix Table 8**, available at www.annals.org). From these lists, we identified therapeutic techniques that most leaders in the profession deemed inappropriate for treatment of participants in these trials. We also identified techniques that, for purposes of our research protocol, we wanted to exclude or limit (for example, acupressure, which is based on meridian theory, was an excluded technique for massage therapists). These lists were then compared with practitioners' self-reported practice patterns to help identify practitioners for our trials. This approach can be individualized to address local needs of medical groups or institutions.

Although many insurance networks use the minimum (and some of the optional) requirements, ideally, academic health centers should seek input from appropriate professional organizations (**Appendix Table 9**, available at www.annals.org), pharmacy and therapeutics committees, and legal counsel to refine their requirements and create reproducible quality-assurance standards across affiliated hospitals.

DISCUSSION

Most CAM professions lack the consistency and uniformity of licensing and credentialing processes of other health care professions. If insurers increasingly reimburse for CAM therapies, patient utilization is likely to increase (53). It is also likely that with increased legislative and judicial acceptance of CAM therapies, reimbursement for these therapies will increase (44). Yet, social forces create an uneven map of licensure and legally authorized scope of practice across both CAM professions and states (9). This in turn creates a complex, uncertain terrain for many clinicians for whom homogeneity of education and training is the sine qua non for referring or comanaging patients. Furthermore, physicians face ethical dilemmas in providing referral advice or CAM services in the absence of definitive data regarding documented risks and benefits (54).

More uniform, nationwide standards for licensing and credentialing of CAM providers could help facilitate responsible physician collaboration and referral; offer more authoritative, consistent, and generalizable clinical and financial research; minimize access to unqualified CAM providers; and help translate CAM therapies into standardized diagnostic and therapeutic codes for billing purposes. With greater standardization, clearer practice standards could be established and hospital credentialing and regulation be made more responsive to consumer needs. Both observational monitoring and controlled scientific investigation that is capable of delivering authoritative (and generalizable) results could also be facilitated.

Such changes would help increase public trust, practitioner rigor, legislative integrity, research capabilities, and patient access to a range of "credentialed" CAM providers and therapies. Indeed, the Select Committee on Science and Technology of the United Kingdom House of Lords recommended that CAM training "become more standardized and be accredited and validated by the appropriate professional bodies" (55–57).

Clearer credentialing of CAM providers would also facilitate risk management by health care institutions dedicated to responsible integration of such therapies. At present, although there are few, if any, reported judicial opinions involving lawsuits against physicians who refer to or comanage patients with licensed CAM providers (43, 58), such lawsuits are likely to occur more often as CAM therapies are increasingly incorporated within conventional medical delivery systems (43, 44).

At the same time, greater homogeneity may undermine the diversity of education, training, and skill, which historically have characterized many CAM professions. The result may be excessive standardization, rigid scope of practice boundaries, excessive utilization standards (number of visits) and fee schedules, increases in patient volume, decreases in individualization of services, a decrease in time spent per patient, and a perceived decrease in satisfaction by both patients and CAM practitioners.

More standardized licensing and credentialing for CAM therapies might also alienate CAM providers. Many CAM providers lack the resources to establish the needed infrastructure to operate in a tightly regulated environment, with constraints by third-party payers and other administrative requirements. Many CAM providers fear that with the development of national standards for quality assurance, credentialing, scope of practice, and reimbursement, they will end up 1) subordinate to medical doctors, as has been the case with some conventional nonphysician providers, such as physical therapists; 2) unsatisfied with their professional practices, as are many health care providers in today's highly regulated and managed environment; 3) reimbursed at a lower rate than if paid by fee-for-service; 4) violating the core philosophy of their practices; and 5) further burdened by administrative work. In summary, many CAM providers question whether more uniform licensing and credentialing standards, even if feasible, would be desirable.

CONCLUSION

Despite the historical divide between medical doctors and CAM providers, the present legal landscape permits widespread practice of CAM therapies. This observation—that legal recognition trumps medical recognition—also suggests other interactions between medical–scientific and legal processes. First, legislative (and judicial) processes may override medical opinions on the relative efficacy and value of CAM therapies. This will occur although even credentialed providers can deliver ineffective therapy. Second, in the eyes of clinicians sworn to do no harm, safety trumps efficacy and must be paramount; yet, in the eyes of many health care consumers and their elected representatives, freedom of choice not uncommonly trumps scientific or medical acceptance or evidence of safety. Third, while evidence-based conclusions guide medical advice and practice, the perspectives and practices of many CAM providers are based on vitalistic, spiritual, and cultural understandings of health and disease (59), which may thereby influence legislative decisions. Fourth, when a physician refers a patient to (or comanages the patient with) a licensed CAM provider, increased communication with both the patient and the CAM provider regarding the CAM provider's qualifications and treatment plan may improve the physician–patient relationship and also decrease the prospect of adverse events and malpractice litigation (6, 43, 44).

Finally, larger social forces temper and mediate the entire debate. Thus, particular issues in credentialing, such as turf battles between professions over scope of practice, reflect larger cultural and political collisions concerning the evolving definitions of mainstream medical care. Such issues also reflect fundamental philosophic questions as to who determines which providers and therapies will be accepted as safe, effective, appropriate, or reimbursable. Legislative recognition may trump medical recognition; however, scientific evidence ultimately informs both legislative and medical behavior (as well as third-party reimbursement). These "checks and balances" are essential to the ongoing refinement of our medical delivery system.

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Information on the various health professions changes rapidly. The figures in this article represent a snapshot of the profession [as reported by the professions or their representatives] at various dates before acceptance of this article for publication.

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2002–2003 Series: Update Sessions from ACP–ASIM's 2002 Annual Session
David A. Cramer, MD, and Paul T. Kefalides, MD, Co-Editors

Update in Infectious Diseases

Bennett Lorber, MD

A look at the medical literature from 2001 affirms that infectious diseases remains one of the most changeable and exciting areas of clinical practice. The papers I review in this Update cover terrorist threats to the public health, new approaches to some old problems, newly recognized disorders and novel treatments for infection, HIV infection, and infectious complications of treatment for other illnesses.

Biological Terrorism

Bioterrorism in the United States is no longer merely a threat but a reality; Americans ask not "What if?" but "What next?" Bioterrorism, as distinct from biological warfare, is an attempt not so much to kill and incapacitate but to cause panic and disrupt daily life. To date, 7 cases of cutaneous anthrax and 11 cases of inhalational anthrax from terrorist activity have been confirmed.

The Unthinkable Happens: The Initial Cases of Terrorism-Related Inhalational Anthrax

Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. Emerg Infect Dis. 2001;7:933-44. [PMID: 11747719]

Eight of the first 10 victims of inhalational anthrax were postal workers exposed when they processed letters containing spores of *Bacillus anthracis*. After a 4- to 6-day incubation period, the victims developed fever, chills, fatigue, and malaise and often had drenching sweats and a nonproductive cough. Severe dyspnea, nausea, vomiting, and pleuritic pain were frequent. Many patients had elevated liver enzyme levels and were hypoxic. Chest radiographs were consistently abnormal, showing a widened mediastinum, infiltrates, and pleural effusion. Seven patients had positive blood cultures. With multidrug antimicrobial therapy and supportive care, 6 of the 10 patients survived.

Most patients had an increase in neutrophil counts or the number of immature neutrophils. Every patient had pleural effusion within 24 hours of presentation. An initial nonspecific phase was followed within 3 days or less by rapidly worsening shortness of breath, stridor, and sometimes stupor.

Up to half of patients with anthrax develop hemorrhagic meningitis, and death often occurs within 24 to 36 hours of onset of symptoms. Treatment begins with intravenous ciprofloxacin or doxycycline in addition to one or two other drugs. Clindamycin, which shuts down toxin production, should be one of these. Meningitis may respond to the addition of vancomycin, rifampin, or chloramphenicol. Whether to give steroids remains an open question. Oral agents may be introduced when the patient is stable; treatment lasts 2 months. The U.S. Food and Drug Administration has approved ciprofloxacin for anthrax treatment. All the quinolone antibiotics are very active in vitro.

New Insights into Common Infections

Women Successfully Diagnosed and Treated Their Own Recurrent Urinary Tract Infections

Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Ann Intern Med. 2001;135:9-16. [PMID: 11434727]

In this prospective, uncontrolled study, 172 women who had at least two urinary tract infections (UTIs) in the past 12 months were taught to obtain clean-catch urine specimens. They were given six 200-mg tablets of ofloxacin to take twice a day for 3 days for new symptoms suggestive of UTI. Later in the trial, the authors changed the intervention to one 250-mg tablet of levofloxacin given once daily for 3 days. About half the women self-diagnosed at least one UTI during a mean follow-up of 8 months; a total of 172 episodes occurred. For the 84% of women for whom urinalysis and urine culture identified a uropathogen, the clinical cure rate was 92% (**Figure**). The microbiological cure rate was 96%. The participants were highly satisfied with the regimen, and the study medication caused no serious adverse effects.

Women with recurrent UTIs often are advised to take one of several prophylactic low-dose antimicrobial regimens (administered after sexual intercourse, three times per week, or daily). These regimens result in unnecessary treatment for women with infrequent or clustered infectious episodes. Self-diagnosis and self-treatment offer a safe, timely, and effective alternative for reliable patients. Those affected need not visit a health care provider.

Manges and colleagues (1) report on another aspect of UTI; they found that 51% of 55 *Escherichia coli* isolates from female students at a California university who reported UTIs resistant to trimethoprim–sulfamethoxazole belonged to clonal group A. The corresponding figure for a control group of 50 isolates sensitive to this antimicrobial

Ann Intern Med. 2002;137:974-980.
For author affiliation, see end of text.

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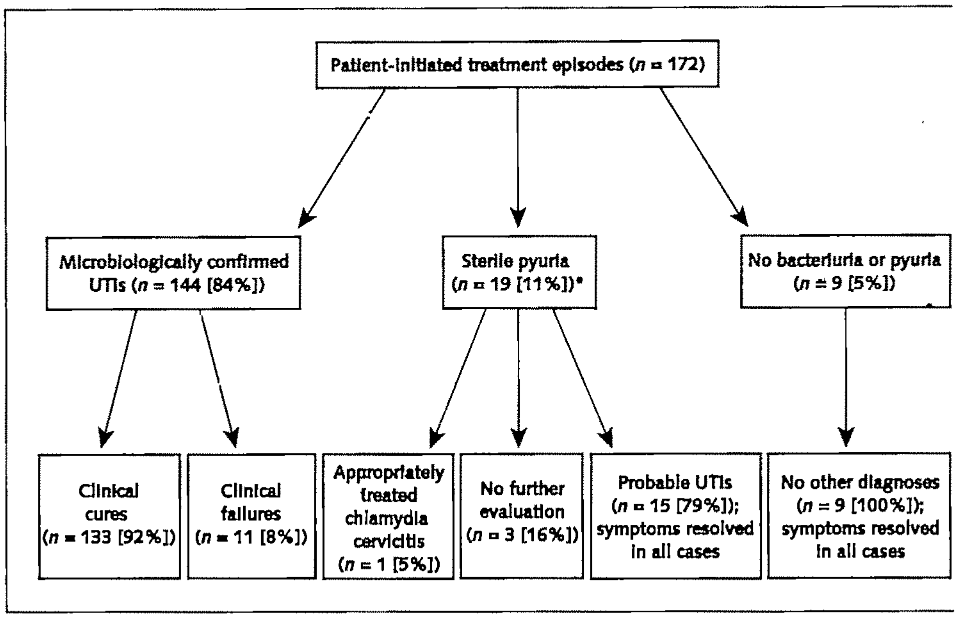
Figure. **Diagnostic accuracy and outcomes of 172 patient-initiated treatment episodes of recurrent urinary tract infection (*UTI*).**


Patient-initiated treatment episodes (*n* = 172)
Microbiologically confirmed UTIs (*n* = 144 [84%])
Sterile pyuria (*n* = 19 [11%])*
No bacteriuria or pyuria (*n* = 9 [5%])
Clinical cures (*n* = 133 [92%])
Clinical failures (*n* = 11 [8%])
Appropriately treated chlamydia cervicitis (*n* = 1 [5%])
No further evaluation (*n* = 3 [16%])
Probable UTIs (*n* = 15 [79%]); symptoms resolved in all cases
No other diagnoses (*n* = 9 [100%]); symptoms resolved in all cases

*Sterile pyuria was defined as ≥10 leukocytes per high-power field. Reproduced from Gupta et al. Ann Intern Med. 2001;135:9-16.

combination was 4%. Clonal group A organisms accounted for 11% of all UTIs during the 4-month study. Almost 40% of resistant isolates from similar cohorts in Michigan and Minnesota also belonged to clonal group A. The clonal consistency of uropathogens in three widely separated college communities suggests that they may have been introduced through eating contaminated food and that UTIs, currently believed to occur sporadically, sometimes may occur as community-wide outbreaks. This could become a serious public health problem.

Timely Single-Dose Doxycycline Therapy Can Prevent Lyme Disease

Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. N Engl J Med. 2001;345:79-84. [PMID: 11450675]

This randomized, double-blind, placebo-controlled trial evaluated a single 200-mg dose of doxycycline in 482 persons living in an area of New York State where Lyme disease is hyperendemic. Each person had removed attached *Ixodes scapularis* ticks from his or her body in the past 3 days. Erythema migrans developed in 3.2% of controls but in only 0.4% of persons given doxycycline. Prophylaxis was 87% effective, but at a cost: Thirty percent of treated person had side effects compared with 11% of controls. Nausea and vomiting were the most common problems. No extracutaneous disease was diagnosed in either group, nor did any asymptomatic seroconversions occur.

Cases of Lyme disease have increased steadily over the past two decades. Those clustered in a few small regions account for an estimated 90% of all cases in the United States. Not only did a single dose of doxycycline prevent the Lyme disease rash, but no person without symptoms seroconverted. This approach may be especially well suited for use in hyperendemic areas. Because the infection rate following a tick bite is low, however, and because all persons in this study who became infected developed a rash, an alternative is to advise those bitten by a tick to seek help if erythema migrans develops.

Antibiotic Therapy for Chronic Symptoms Following Lyme Disease Is Not Useful

Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001;345:85-92. [PMID: 11450676]

After treatment for acute Lyme disease, some patients develop chronic symptoms such as musculoskeletal pain, neurocognitive symptoms, dysesthesia, and fatigue. Klempner and colleagues asked whether prolonged antimicrobial therapy helps these patients. Their placebo-controlled trial of intravenous ceftriaxone, 2 g/d for 1 month, followed by oral doxycycline, 200 mg/d for 2 months, found that prolonged treatment provided no further benefit. As a result, the study was discontinued. Clearly, it is unwise to expose the small minority of patients who have chronic sequelae of Lyme disease to the potential health risks and costs of long-term antimicrobial therapy.

Oseltamivir Prevents Influenza in Household Contacts

Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA. 2001;285:748-54. [PMID: 11176912]

Can oseltamivir, an orally active neuraminidase inhibitor active against both influenza A and influenza B, prevent infection of household contacts and thereby contain the spread of infection to the community? This double-blind, placebo-controlled trial randomly assigned 955 household contacts to receive either 75 mg of oseltamivir or placebo within 48 hours of symptom onset in the index patient. Treatment continued for 1 week. As assessed by viral shedding in nose–throat swabs or a fourfold increase in specific antibody, the overall protective efficacy of oseltamivir was 89% in contacts and 84% in households. The drug was extremely well tolerated. The message from this study is that postexposure prophylaxis is safe and does work.

Emerging and Reemerging Infections

New York City, 1999: West Nile Virus First Appears in the Western Hemisphere

Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001; 344:1807-14. [PMID: 11407341]

The 59 patients hospitalized with West Nile virus infection in the New York City region in August and September 1999 represented an attack rate of at least 6.5 cases per 1 million persons. The median patient age was 71 years, and the attack rate increased sharply with advancing age. More than 60% of patients had clinical meningoencephalitis, and 12% of the patients died. (Young people rarely die of this illness.) About one fourth of patients had muscle weakness, and 10% had flaccid paralysis caused by axonal polyneuropathy. Two factors, diabetes and an age of 75 years or older, independently predicted death; the respective relative risk estimates were 5.1 and 8.5. Underlying chronic medical conditions were frequent in this population, including hypertension in 42% of patients, diabetes and coronary artery disease in 20% each, and immunosuppression related to cancer and other factors in 14%.

Patients given a diagnosis of West Nile virus infection frequently have participated in outdoor activities in the evenings. This, the first such outbreak in the Western Hemisphere, coincided with the deaths of thousands of crows, some of whose tissue specimens yielded West Nile virus. The virus has also been isolated from mosquitoes, horses, and small mammals. During the time of this study, West Nile virus caused 27% of cases of encephalitis with muscle weakness, 14% of cases of isolated encephalitis, and 6% of cases of aseptic meningitis. A key to diagnosing the infection is recognizing an association of muscle weakness or flaccid paralysis with encephalitis in an older person. Human infections have been documented all along the East Coast of the United States and now are spreading westward. The geographic range of this arboviral illness is likely to spread, calling for close mosquito surveillance and control.

Active Tuberculosis Developed after Initiation of Infliximab Therapy

Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098-104. [PMID: 11596589]

Infliximab, a humanized antibody that neutralizes tumor necrosis factor-α, is used to treat rheumatoid arthritis and Crohn disease. An estimated 147 000 patients worldwide have received this agent, and, as of mid-2001, 70 reports had described tuberculosis developing a median of 12 weeks after the start of infliximab treatment. Most patients had received three or fewer infusions at the time tuberculosis was diagnosed. Forty patients had extrapulmonary disease, and 17 had disseminated disease. Of 12 deaths, at least 4 were ascribed to tuberculosis.

Many of these tuberculosis cases occurred in areas with a low incidence of the disease. In patients given infliximab, tuberculosis has developed much more often than other opportunistic infections. Physicians should screen for tuberculosis before prescribing this agent.

Treatment for Latent Tuberculosis Was Associated with Severe, Even Fatal, Liver Injuries

Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. MMWR Morb Mortal Wkly Rep. 2001;50:733-5. [PMID: 11787580]

During a 6-month period in 2001, the Centers for Disease Control and Prevention learned of 21 patients who developed liver injury after starting a 2-month regimen of rifampin and pyrazinamide for latent tuberculosis infection. Three patients had previously recovered from isoniazid-related liver injury. Including two previously reported cases, 6 of 23 patients died of liver failure. Severe liver damage has occurred despite monitoring of liver function and discontinuation of the rifampin–pyrazinamide regimen at the first sign of liver toxicity.

The safest policy is to avoid this regimen altogether. If that is unavoidable, the physician should follow the recommendations offered jointly by the American Thoracic Society and Centers for Disease Control and Prevention: 1) Be especially cautious in prescribing rifampin–pyrazinamide if a patient is alcoholic or is taking other hepatotoxic drugs; 2) avoid the regimen if the patient has underlying liver disease or a history of isoniazid toxicity; 3) dispense no more than a 2-week supply of medication; 4) instruct patients to stop treatment if they develop abdominal pain, vomiting, or jaundice; 5) monitor aminotransferase and bilirubin levels before starting treatment and after 2, 4, and 6 weeks of treatment; and 6) stop treatment if the aminotransferase level is more than five times the upper limit of normal (or is above normal to any extent if the bilirubin level is also elevated or the patient has symptoms of hepatitis).

Tick-Borne Rickettsial Pathogen Threatens African Travelers

Raoult D, Fournier PE, Fenollar F, et al. *Rickettsia africae*, a tick-borne pathogen in travelers to sub-Saharan Africa. N Engl J Med. 2001;344:1504-10. [PMID: 11357153]

Rickettsia africae caused a febrile illness in 133 of 417 persons who returned from a trip to sub-Saharan Africa or Guadeloupe; 39 had direct evidence of infection (polymerase chain reaction assay or cell culture), and 94 had a specific serologic response. Most had a mild illness. Nearly half the patients had a maculopapular or vesicular rash. Forty-four percent of the group reported tick exposure, and 54% had multiple eschars (papular lesions with a central scab), an unusual finding in rickettsial infection and an important clue to the diagnosis. Most patients received doxycycline for 1 to 2 weeks. Sixteen percent received no treatment and also did well.

Visitors to Acapulco Were at Risk for Pulmonary Histoplasmosis

Update: outbreak of acute febrile respiratory illness among college students—Acapulco, Mexico, March 2001. MMWR Morb Mortal Wkly Rep. 2001;50:359-60. [PMID: 11465910]

More than 200 college students developed pulmonary histoplasmosis after visiting Acapulco, Mexico, in the spring of 2001. Most developed fever, chills, a dry cough, chest pain, and headache. Computed tomography of the chest typically showed multiple nodules in both lung fields. A silver-stained bronchoalveolar lavage specimen showed *Histoplasma capsulatum*. Staying at a particular hotel (now closed) was implicated as a risk factor. This experience reinforces the importance of asking anyone with acute febrile illness about recent travel.

Malarial Deaths Followed Improper Chemoprophylaxis

Malaria deaths following inappropriate malaria chemoprophylaxis—United States, 2001. MMWR Morb Mortal Wkly Rep. 2001;50:597-9. [PMID: 11476528]

This cautionary report describes malarial deaths in two Americans who visited countries harboring chloroquine-resistant *Plasmodium falciparum*. One person took chloroquine alone, and the other took both chloroquine and proguanil. The Centers for Disease Control and Prevention explicitly does *not* recommend chloroquine-containing regimens for travelers whose destination is a country, often in sub-Saharan Africa, where resistance to chloroquine is widespread. In these circumstances, mefloquine and doxycycline are preferred; an alternative is Malarone (GlaxoSmithKline, Research Triangle Park, North Carolina), a combination of atovaquone and proguanil. Chloroquine is, in fact, an effective prophylactic agent in only a few areas of the world. A review of 4685 cases of imported malaria (that is, acquired outside the United States but diagnosed in the United States) reported from 1992 through 2001 showed that 19% of patients used inappropriate prophylaxis and 56% used no prophylaxis.

The Pseudomonas "Hot-Foot" Syndrome Developed after Exposure to Coated Pool Floor

Fiorillo L, Zucker M, Sawyer D, Lin AN. The pseudomonas hot-foot syndrome. N Engl J Med. 2001;345:335-8. [PMID: 11484690]

Fiorillo and colleagues reported that extremely painful nodular skin lesions developed on the soles of the feet of 40 children who used a community wading pool in Canada; the floor of the pool had been coated with an abrasive material to prevent slipping. The lesions, representing a new clinical entity, developed within 10 to 40 hours after exposure and consistently resolved within 2 weeks. Only 3 patients received antibiotic treatment. Three had recurrences after again using the wading pool. Identical isolates of *Pseudomonas aeruginosa* were present in skin lesions and pool water. This syndrome is the latest form of skin infection associated with hot tubs, saunas, whirlpools, hydrotherapy pools, and water slides in recreational parks.

HIV Infection

When Can Prophylaxis against *Pneumocystis carinii* Pneumonia Be Safely Discontinued?

Lopez Bernaldo de Quiros JC, Miro JM, Peña JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med. 2001;344:159-67. [PMID: 11172138]

Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is indicated for HIV-infected patients whose CD4 cell count decreases to less than 200 cells/mm^3 (as well as those with previous PCP). However, the consequences of withdrawing prophylaxis after a favorable response to highly active antiretroviral therapy are unclear. This randomized trial by Lopez Bernaldo de Quiros and colleagues showed that withdrawing prophylaxis is safe. Patients who had an increase in CD4 count to greater than 200 cells/mm^3 for at least 3 months were studied. Among 474 patients receiving treatment with at least three antiretroviral drugs—one of them a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor—none of the 240 who discontinued primary prophylaxis developed PCP during a median follow-up of 20 months. Among 113 patients given secondary prophylaxis, none of 60 randomly assigned to discontinue it had an episode of PCP during median follow-up of 12 months. Prophylaxis may be safely withdrawn when the CD4 cell count remains greater than 200 cells/mm^3 for more than 3 months, even if viral replication continues. At least one fourth of the patients in this study had detectable HIV.

In a multicenter observational study (2), secondary prophylaxis was stopped in 325 patients whose CD4 cell count exceeded 200 cells/mm^3. Episodes of PCP episodes did not recur during a median 13-month follow-up. This experience corroborates the results of Lopez Bernaldo de Quiros and colleagues' randomized trial of withdrawing prophylaxis. Only 5% of patients resumed prophylaxis because of a decline in CD4 cell count. These two studies affirm the safety of withdrawing PCP prophylaxis. The benefits include less toxicity, less inconvenience for patients, and lower costs.

Should Antiretroviral Treatment Be Discontinued when Viremia Persists?

Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N Engl J Med. 2001;344:472-80. [PMID: 11172188]

This small-scale study examined the consequences of withdrawing combination antiretroviral therapy, including protease inhibitors, in HIV-infected patients despite plasma HIV RNA levels exceeding 2500 copies/mL. In 11 patients the CD4 cell count initially declined as the plasma HIV RNA level increased. In all patients with infection initially resistant to treatment, the virus became susceptible to protease inhibitor therapy within 16 weeks of withdrawal. However, resistant virus was present in 5 of 9 patients whose blood mononuclear cells were cultured for HIV. Virus replication, which initially was low, increased after withdrawal of treatment. All these measures remained stable in 5 control patients who were assigned to continue treatment. Three patients had significant adverse events after discontinuing treatment: PCP, disabling peripheral neuropathy, and severe thrombocytopenia, respectively.

These findings suggest that stopping antiretroviral treatment in the face of apparent treatment failure, as indicated by persistent detectable viremia, may lead to emergence of a wild-type virus that is better able to replicate and decrease CD4 cells in peripheral blood. Clinical deterioration is a distinct possibility.

Co-Infection with GB Virus C Promotes Survival of HIV-Infected Patients

Xiang J, Wünschmann S, Diekema DJ, et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. N Engl J Med. 2001;345:707-14. [PMID: 11547739]

GB virus C (GBV-C), also known as hepatitis G virus, is a flavivirus that, although related to hepatitis C virus, does not cause liver disease. Reports suggesting that HIV-infected persons who are co-infected by GBV-C progress less rapidly to AIDS prompted a survey of 362 HIV-positive patients, 40% of whom had GBV-C viremia. After adjustment for possible confounding factors (including treatment for HIV infection and the CD4 cell count), mortality was significantly higher—56.4% vs. 28.5%—in patients not co-infected by GBV-C during an average follow-up of 4 years (relative risk, 3.7 [95% CI, 2.5 to 5.4]). GB virus C reliably inhibited HIV replication in blood mononuclear-cell cultures but did not alter the expression of HIV surface receptors.

A corroborative study of 197 prospectively followed HIV-positive patients found that those testing positive for GBV-C RNA (17% of the group) took longer to develop AIDS and lived significantly longer after AIDS was diagnosed (3). Patients given highly active antiretroviral treatment had the same result. The effect of GBV-C was independent of the CD4 cell count. The GBV-C load correlated inversely with the HIV load. Discovering the mechanism of this effect, which is currently unknown, might lead to new approaches to treating HIV disease.

How Can Undertreating HIV-Infected Women Be Avoided?

Sterling TR, Vlahov D, Astemborski J, et al. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. N Engl J Med. 2001;344:720-5. [PMID: 11236775]

In men, the initial HIV load after seroconversion predicts the likelihood that AIDS will develop. To learn whether initial HIV load is a predictor of AIDS in women, Sterling and colleagues prospectively followed 156 male and 46 female users of injected drugs after seroconversion. The median initial viral load was more than three times greater in men than in women (51 000 copies/mL vs. 15 000 copies/mL), but men and women had similar CD4 cell counts and progressed to AIDS at a similar rate. According to the recommendation that treatment should begin when the viral load reaches 20 000 copies/mL, 74% of men but only 37% of women would have been eligible for treatment at the first postseroconversion visit. If treatment were initiated only when the viral load was greater than 20 000 copies/mL, many women who would benefit from therapy would not have been treated.

When Should Antiretroviral Treatment Begin?

Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA. 2001;286:2560-7. [PMID: 11722270]

Does delaying the start of antiretroviral therapy compromise the therapeutic response in patients with HIV infection? To answer this question, Phillips and colleagues followed more than 3200 previously untreated HIV-positive patients for a median of 30 months during treatment with at least three drugs. In 85% of patients, viral load decreased to less than 500 copies/mL. Neither a lower baseline CD4 cell count nor a higher viral load at baseline was associated with a less favorable virologic outcome. Viral suppression took longer in patients whose baseline viral load exceeded 100 000 copies/mL. These findings imply that delaying treatment may not jeopardize HIV suppression.

Another study (4) demonstrated consistently low rates of progression to AIDS or death in 1219 newly treated HIV-positive men who were given triple-drug therapy. The crude AIDS-related mortality rate was 6.7%. In multivariate analysis, only the baseline CD4 cell count was significantly associated with mortality. Compared with patients whose CD4 cell counts were 200 cells/mm^3 or greater, patients with counts less than 50 cells/mm^3 were 6.7 times more likely to die and those with counts of 50 to 199 cells/mm^3 were 3.4 times more likely to die.

Together, these studies tell us that it is reasonable to delay HIV therapy until the CD4 cell count approaches 200 cells/mm^3, regardless of the virus level in plasma.

Treatment: Effects and Side Effects

Infusing Activated Protein C Reduced Septic Deaths, but at a Price

Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699-709. [PMID: 11236773]

The activated form of protein C, a serine protease made in the liver, has antithrombotic and anti-inflammatory properties and promotes fibrinolysis. Serum levels of activated protein C decrease in sepsis. In previous studies, recombinant human activated protein C, also known as drotrecogin-α, has dose-dependently reduced levels of markers for coagulation and inflammation in patients with severe sepsis. Bernard and colleagues' randomized, double-blind, placebo-controlled trial assigned 1690 patients with systemic inflammation and organ failure from acute infection to a 96-hour infusion of drotrecogin-α (24 μg/kg of body weight per hour) or placebo. The lungs and abdomen were sites of infection in nearly three fourths of patients, and about the same proportion had two or more dysfunctional organs or systems. The mortality rate was 31% in placebo recipients and 25% in patients given drotrecogin-α. The relative risk for death declined by 19.4% (CI, 6.6% to 30.5%), while the absolute risk decreased by 6% ($P = 0.005$). The authors estimated that 1 life would be saved for every 16 patients treated. Severe adverse events were similar in the two groups, except that serious bleeding was more frequent in actively treated patients (3.5% vs. 2.0%) and occurred during the infusion period.

This study was stopped early because of the substantial difference in mortality between groups. Drotrecogin is one of a group of drugs called "cogins" (for *co*a*g*ulation and *in*flammation). It has been approved by the Food and Drug Administration and commercially released. In this trial, the agent helped only the most seriously ill patients. It is important to note that the study design excluded patients at an increased risk for bleeding, such as those who had recently undergone surgery or those requiring dialysis. Whether postmarketing studies will affirm the utility of activated protein C treatment is unknown. The treatment costs almost $7000 per course, and hospitals will have to use strict criteria for treatment. The increased risk for bleeding is especially troubling because, with two exceptions, bleeding in particularly dangerous sites (12 instances of intracranial, intrathoracic, and retroperitoneal bleeding) occurred only in actively treated patients.

Caspofungin Is a Novel Antifungal Agent

Caspofungin, the first of a new class of antifungal drugs called *echinocandins*, is active in vitro and in vivo against *Aspergillus* species and all clinically important *Candida* species. These drugs inhibit the synthesis of essential parts of the fungal cell wall. Caspofungin must be given intravenously; the suggested initial dose is 70 mg, followed by 50 mg/d. The dose need not be adjusted in patients who have renal failure or are receiving dialysis. Co-treatment with several drugs, such as rifampin, phenytoin, carbamazepine, and dexamethasone, reduces circulating levels of caspofungin by about 20%. Thus, the maintenance dose should be 70 mg (5). Cyclosporine, in contrast, increases caspofungin levels by 35%.

Caspofungin appears to be a safe antifungal agent with no apparent nephrotoxic effects. About 15% of patients taking the drug have mild increases in aminotransferase activity. In 2001, the Food and Drug Administration approved caspofungin as a second-line agent for invasive aspergillosis. The drug should also prove to be an effective treatment for candidiasis (5, 6). This agent should be especially useful in patients with life-threatening fungal infection who cannot tolerate amphotericin B or who harbor *Candida* species that are resistant to an azole drug.

Survey Found No Relation between Vaccinations and Multiple Sclerosis

Confavreux C, Suissa S, Saddier P, et al. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. N Engl J Med. 2001;344:319-26. [PMID: 11172162]

Physicians have long been concerned that vaccination may either precipitate the onset of multiple sclerosis or promote relapse. Recent reports from France have suggested an increased risk for active multiple sclerosis following vaccination against hepatitis B virus. Confavreaux and colleagues' case-crossover study chronicled information on vaccinations for 643 European patients with multiple sclerosis who experienced a relapse from 1993 through 1997. The rate of reported vaccination within the past 12 months was 15%, and nearly 95% of these reports were confirmed. The relative risk for relapse associated with any vaccination in the previous 2 months was 0.71 (CI, 0.40 to 1.26). The risk for relapse was not associated with vaccination against tetanus, hepatitis B, or influenza viruses. The investigators concluded that common vaccinations do not make multiple sclerosis more likely to relapse. Another well-designed study (7) gave no indication that the risk for either initial multiple sclerosis or relapse is associated with hepatitis B virus vaccination. Given the relatively small risk for relapse during the study period, the available data do not support an association between vaccination and multiple sclerosis; however, they do not exclude the possibility that a larger study or a longer study might show a small association. Both of these studies should reassure clinicians and the public that vaccines for hepatitis B virus and other infectious agents are unlikely to cause multiple sclerosis in healthy individuals and will not precipitate relapse in patients who have already received a diagnosis of multiple sclerosis.

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Novel Insights in the Congenital Long QT Syndrome

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Background: The congenital long QT syndrome is a potentially fatal, inherited cardiac syndrome. Early diagnosis and preventive treatment are instrumental to prevent sudden cardiac death in patients with the congenital long QT syndrome.

Purpose: To review new insights in genetics and cellular electrophysiology, as well as the current understanding of the clinical diagnosis and treatment of the congenital long QT syndrome.

Data Sources: Authors' personal databases and search of PubMed database from 1966 to 2001.

Study Selection: Experimental and clinical studies on the congenital long QT syndrome.

Data Extraction: Data from peer-reviewed studies were manually extracted, classified, and summarized.

Data Synthesis: The congenital long QT syndrome is characterized by abnormally prolonged ventricular repolarization, which predisposes patients to syncope, ventricular arrhythmias, and sudden cardiac death. The recent discovery of mutations in genes encoding ion channels has improved our understanding of the cellular origin of this condition. The congenital long QT syndrome may result from inherited defects in cardiac K^+ and Na^+ channels, which both result in prolongation of the ventricular action potential. The diagnosis is based on electrocardiographic and clinical criteria. Genetic screening of symptomatic patients or asymptomatic family members may identify patients at risk for life-threatening ventricular arrhythmias. β-Blocking agents are the mainstay of treatment. Certain patients may also benefit from a pacemaker or implantable cardioverter defibrillator. Recent studies suggest that genotype-specific treatment of the congenital long QT syndrome will be feasible in the near future.

Conclusions: The congenital long QT syndrome is a potentially life-threatening condition caused by mutations in genes encoding cardiac ion channels. Better understanding of the mechanisms responsible for this condition will guide genotype-specific therapy in the near future.

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Over the past decade, the discovery of mutations in genes encoding ion channels (1) has helped researchers to better understand the mechanism of the congenital long QT syndrome, an inherited disease characterized by prolonged ventricular repolarization and a propensity for life-threatening ventricular tachyarrhythmias resulting in syncope and sudden death (2). Current estimates suggest that 1 in 10 000 persons are gene carriers and that the congenital long QT syndrome causes 3000 to 4000 sudden deaths in children and young adults each year in the United States (3). The two major clinical syndromes characterized on the basis of the genetic transmission pattern are a more common autosomal-dominant form (the Romano–Ward syndrome) with a pure cardiac phenotype (4, 5) and a rarer autosomal-recessive form (the Jervell and Lange–Nielsen syndrome) characterized by the association with congenital neuronal deafness (6). The congenital long QT syndrome occurring secondary to electrolyte disturbances or drug therapy is called the acquired long QT syndrome (7).

As a consequence of the genetic information, it became clear that what has been classified under the unifying name "long QT syndrome" actually represents many different diseases caused by ion channel mutations; these mutations produce alterations in ionic currents, leading to the same result: prolonged ventricular repolarization (8). In addition, the first ion channel gene mutations and polymorphisms that predispose people to drug-provoked QT interval prolongation and ventricular arrhythmias have been identified (9, 10).

In this review, we classify the forms of the congenital long QT syndrome; discuss the proposed explanations of the cellular electrophysiology of the syndrome; review the clinical characteristics of the syndrome; and discuss the identification and management of patients with the congenital long QT syndrome, including novel approaches, such as genotype-specific therapies.

METHODS

We searched the PubMed database for literature on the congenital long QT syndrome, focusing on advances in four areas: forms of the congenital long QT syndrome, explanations of the cellular electrophysiology of the syndrome, clinical characteristics of the syndrome, and identification and management of patients with the congenital form of the syndrome. We manually extracted, classified, and summarized data from peer-reviewed studies.

GENETICS OF THE CONGENITAL LONG QT SYNDROME

Genetic linkage mapping of the autosomal-dominant Romano–Ward syndrome has so far identified loci on six chromosomes (*LQT1* to *LQT6*) (11–17). The autosomal-recessive variant (the Jervell and Lange–Nielsen syndrome) arises in individuals who inherit abnormal *KCNQ1* (= *KvLQT1*) or *KCNE1* (= *minK*) alleles from both parents (*LQT1*, *LQT5*). The abnormal gene can be the same (usually in consanguineous families) or different (so-called compound heterozygosity) (18). Parents of individuals with the Jervell and Lange–Nielssen syndrome are heterozygous for long QT syndrome mutations but are usually (but not always) asymptomatic (19). Most long QT syndrome genes encode K^+ channels; the exception is the

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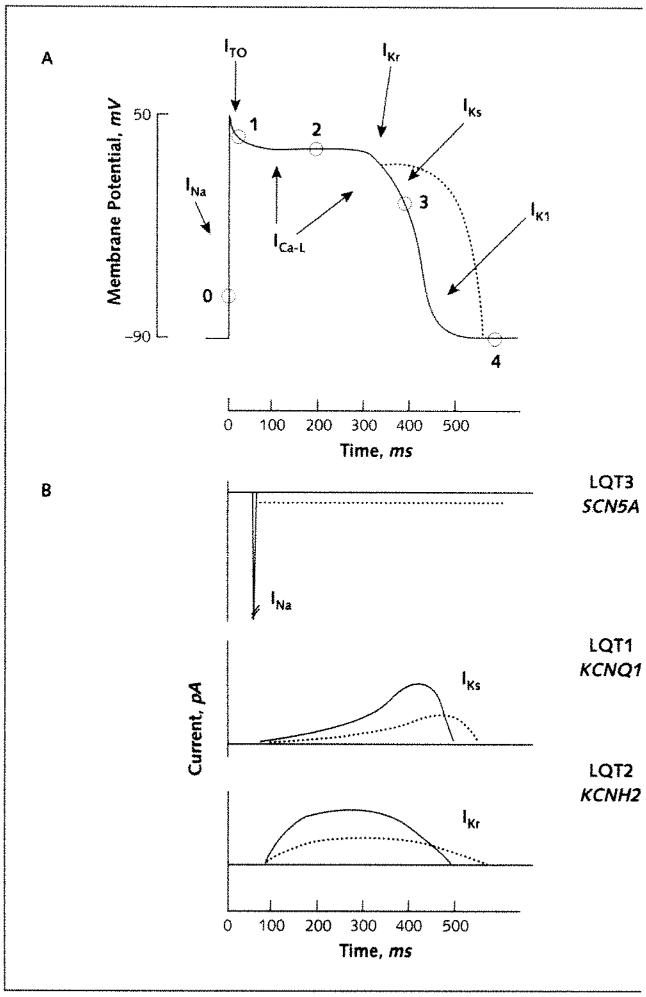
Figure 1. **Ventricular action potential and electrophysiologic effects of the congenital long QT syndrome ion channel mutations.**



A. The ventricular action potential is initiated by current flow through cardiac Na^+ channels (depolarization, phase 0). Early repolarization (phase 1) is caused by the K^+ current I_{TO}. The action potential plateau phase (phase 2) is maintained by $I_{Ca,L}$, I_{Kr}, and I_{Ks} currents, and late repolarization (phase 3) is caused by current flow through I_{Ks} and I_{K1} channels. The dotted line represents action potential prolongation, as can be observed in the congenital long QT syndrome. **B. Top.** In case of *LQT3*, most mutations in the *SCN5A* gene cause a small noninactivating sodium current that remains active during the action potential plateau phase (*dotted line*) and provides an additional depolarizing current, which prolongs repolarization. **B. Middle.** The *KCNQ1* gene encodes the slowly activating delayed rectifier K^+ channel, which conducts the I_{Ks} current. In case of *LQT1* (*dotted line*), reduced I_{Ks} activity leads to action potential prolongation. **B. Bottom.** The *KCNH2* gene encodes the rapidly activating delayed rectifier K^+ channel, which conducts the I_{Kr} current. In *LQT2*, a reduction of I_{Kr} causes prolongation of the repolarization phase (*dotted line*).

LQT3 gene (*SCN5A*), which encodes the cardiac Na^+ channel (current indicated by I_{Na}) (20).

Mutations in either the α-subunit encoded by *KCNQ1* (*LQT1*) or the β-subunit encoded by *KCNE1* (*LQT5*) can cause defects in the I_{Ks} current. Similarly, mutations in the *LQT2* (*KCNH2* = *HERG*) and *LQT6* (*KCNE2* = *MiRP1*) genes encoding the α- and β-subunits of the rapidly activating delayed rectifier K^+ channel I_{Kr}, respectively, may cause the congenital long QT syndrome (17).

FUNCTIONAL CONSEQUENCES OF THE CONGENITAL LONG QT SYNDROME MUTATIONS

The channels carrying the I_{Ks} and I_{Kr} potassium currents are multimeric (15, 16); alleles from both parents are thought to contribute to the channel complexes (21). By using heterologous expression systems such as *Xenopus* oocytes or mammalian cell lines, mutations in *KCNQ1*, *KCNE1*, *KCNH2*, or *KCNE2* expressed alone or in combination with wild-type alleles typically exhibit a “loss of function” (**Figure 1**). The total current carried by the defective potassium channel complexes is impaired by reduced gating or modified channel kinetics. Because potassium channels are tetrameric proteins, there is also the potential for the presence of a single (or more) mutant subunit in a tetramer to disrupt the function of the remaining wild-type subunits (so-called dominant–negative effect) (22–25).

Mutations in the cardiac Na^+ channels linked to *LQT3* generally promote additional Na^+ channel activity during the plateau phase of the action potential, leading to an extra component of inward current (26, 27). This additional inward current would be expected to prolong repolarization and therefore underlie the phenotype in carriers of these *SCN5A* mutations (8, 28). However, this gain-of-function persistent Na^+ current is not observed in all *SCN5A* mutations (29), which implies that heterogeneity in arrhythmogenic mechanisms exists among Na^+ channel–related long QT syndrome (30, 31).

CLINICAL CHARACTERISTICS

The International Long QT Syndrome Registry was started in 1979 to study epidemiologic and genetic characteristics prospectively (32–35). Among (symptomatic) probands, 50% had experienced a first cardiac event by 12 years of age, and by age 40 years the proportion had increased to almost 90% (35). Multivariate analysis identified the following independent risk factors for syncope or sudden cardiac death: congenital deafness, history of syncope, female sex, documented torsade de pointes or ventricular fibrillation, age at first episode, and the long QT syndrome gene affected (34–37). The duration of the corrected QT interval (QTc) was independently associated with the risk for syncope or sudden death during follow-up (35). These results are in line with the finding that prolongation of the QT interval in an apparently healthy population (38, 39) correlates to an increased risk for death. Whether the QTc variability over time correlates with death remains unknown (40).

The Influence of Age and Sex

Since the duration of QT interval is shorter in men than women (41–46), QT prolongation could be diagnosed more often in women. However, after the introduction of the 1993 diagnostic criteria for the congenital long QT syndrome (Table 1) that define sex-specific criteria for QT duration, such bias leading to a female predominance is less likely. Nevertheless, clinical studies consistently report a female predominance (34, 35, 45). In men, the risk for first cardiac events is typically higher in childhood and decreases after puberty, probably because of a regression of QTc duration (42, 44, 45, 49, 50).

The Influence of Pregnancy

Probands with the congenital long QT syndrome are at significant risk for cardiac events during the postpartum period; nearly 10% of probands in the study by Rashba and colleagues (51) experienced their first cardiac event during the postpartum period. The most important factors contributing to this risk may be related to an increase in sympathetic activity (2, 52) or to increased levels of estrogen and progesterone that directly or indirectly influence the number and function of mutant ion channel proteins (53, 54). Treatment with β-blockers can reduce the risk for cardiac events (51).

IDENTIFICATION AND MANAGEMENT OF PATIENTS WITH THE CONGENITAL LONG QT SYNDROME

Sudden death or a history of unexplained syncope in a child or young adult can bring the patient or family member to the clinician's attention. The clinician should perform electrocardiography (ECG) and interview the patient for a family history of syncope and sudden cardiac death. Many mutation carriers are asymptomatic even though they display ECG characteristics of the congenital long QT syndrome. Another group consists of individuals who have been identified as mutation carriers who do not have symptoms or ECG features (21) or intermittently display electrocardiographic signs. We recommend genetic analysis or referral to a specialized combined genetic–cardiology outpatient clinic for these patients because the study of congenital long QT mutations may improve understanding of the pathophysiology of the disease and may help to develop mutation-specific therapies in the near future (55). In addition, a group of patients carries ion channel mutations or polymorphisms that predispose the patients to the drug-induced long QT syndrome (9). The following paragraphs discuss identification and management of these subgroups.

Patients with Symptoms of the Congenital Long QT Syndrome

Symptoms

Inheritance of an affected gene is suggested by vertigo, syncopal attacks, cardiac arrest, and unexplained sudden cardiac death among immediate family members and by family members with definite long QT syndrome. Neurally mediated syncope and epileptic seizures are the most common differential diagnoses (56). A careful history of symptoms and signs can often clarify this diagnostic dilemma.

Table 1. **Diagnostic Criteria for the Congenital Long QT Syndrome***

Criteria	Points
Electrocardiographic findings	
Corrected QT interval	
≥480 ms†	3
460–480 ms†	2
450–460 ms† (in males)	1
Torsade de pointes‡	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age§	0.5
Clinical history	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history‖	
Family members with "definite" long QT syndrome¶	1
Unexplained sudden cardiac death at age <30 y among immediate family members	0.5

* Adapted from Schwartz PJ et al. Circulation. 1993;88:782-4 (47), with permission.
† Corrected QT calculated with Bazett formula ($QTc = QT/\sqrt{RR}$).
‡ No points if patient is taking drugs to favor QT prolongation.
§ Resting heart rate below second percentile for age (48).
‖ The same family member cannot be counted in both family history criteria.
¶ "Definite" long QT syndrome is score ≥4. Scoring: ≤1 point = low probability of long QT syndrome; 2–3 points = intermediate probability.

Sudden cardiac death during sleep should also raise suspicion of the congenital long QT syndrome, particularly the *LQT3* phenotype (57).

The clinical course of the congenital long QT syndrome is largely influenced by the gene affected (36). By age 15 years, almost 60% of patients with *LQT1* have had a cardiac event (syncope, cardiac arrest, or sudden cardiac death) compared with fewer than 10% of patients with *LQT3* (36, 37). The number of cardiac events that occurred up to age 40 years was also higher in patients with *LQT1* (63%) or *LQT2* (46%) than in patients with *LQT3* (18%). In contrast, the likelihood of death during a cardiac event was much higher in patients with *LQT3* (20%) than in those with *LQT1* and *LQT2* (4%) (36) (Table 2). Because of the low number of patients, no data are yet available for patients with *LQT4*, *LQT5*, and *LQT6*.

Triggers for Syncopal Events

In patients with the congenital long QT syndrome, episodes of sudden loss of consciousness are almost always due to torsade de pointes arrhythmias (59). Torsade de pointes is a polymorphic ventricular arrhythmia showing a peculiar ECG pattern characterized by a continuous twisting of the QRS axis around an imaginary baseline (60). An important characteristic of torsade de pointes is its potential for self-termination or deterioration into ventricular fibrillation. This explains why affected patients often survive several syncopal attacks before succumbing to a fatal one. Recently it has become evident that triggers for arrhythmic episodes and syncope also depend on the specific long QT syndrome gene affected (Table 2) (37, 61–63).

Table 2. **Clinical Characteristics in Common Genotypes of Congenital Long QT Syndrome***

Characteristic	Genotype		
	LQT1	***LQT2***	***LQT3***
Gene mutated	*KCNQ1* (= *KvLQT1*)	*KCNH2* (= *HERG*)	*SCN5A*
Current affected	I_{Ks}	I_{Kr}	I_{Na}
Estimated prevalence, %	42	45	8
Events occurring with exercise or emotional stress, %	97	51	39
Exercise-related trigger	+++	+	+
Other triggers	Diving	Loud noise	Sleep/rest
Events before age 10 y, %	40	16	2
Events before age 40 y, %	63	46	18
Median age at first event, *y*	9	12	16
Mean corrected QT interval, *ms*	490 ± 43	495 ± 43	510 ± 48
QT shortening with exercise	Below normal	Normal	Below normal
Efficacy of β-blockade to prevent events	+++	++	+
Efficacy of mexilletine to shorten QT interval	—	+	+++

* Adapted from Wilde AA, Roden DM. Circulation. 2000;102:2796-98 (58), with permission. Clinical data derived from reference 36. +++ = strong association; ++ = moderate association; + = weak association; — = no effect.

In I_{Ks}-related long QT syndrome (*LQT1*), exercise- and stress-related events dominate the clinical picture (50, 61, 64, 65), which is related to activation of the I_{Ks} current by adrenergic stimulation (66). Diving and swimming, as triggers, are almost exclusive for patients with *LQT1* (37, 62). Patients with *LQT3*-associated Na^+ channel mutations are at particularly high risk at rest or asleep because their QT interval is excessively prolonged at slow heart rates (65, 67). This clear distinction between *LQT1* and *LQT3* with respect to exercise-related triggers does not hold for patients with *LQT2*, who tend to display events both at rest and during exercise (61). However, events provoked by auditory stimuli, such as an alarm clock or telephone ringing, almost exclusively occurred in patients with *LQT2* (37, 61, 62, 68, 69). No data are yet available for patients with *LQT4*, *LQT5*, and *LQT6*.

Treatment Options

Symptomatic individuals require treatment (34, 35, 70). It is important to inform patients and their parents about the importance of adherence, as nonadherence exposes patients to increased risk for cardiac events. Frequent counseling of young patients can motivate them to continue to take their medication while they are asymptomatic. On the basis of observations that physical and emotional stress are important triggers for cardiac events in patients with the congenital long QT syndrome (*LQT1* and *LQT2*) (37, 61, 63), nonmedical treatment should also include lifestyle advice and information on certain drugs to avoid because of their potential to prolong QT intervals. Competitive sports should be generally discouraged, but patients usually tolerate recreational sports that do not cause sudden increases in heart rate. Finally, patients are instructed on how to respond to excessive electrolyte loss, for example, during diarrhea or excessive perspiring. Patients are advised to take drinks that contain minerals, such as potassium.

β-Blocker Therapy: Administration of β-blocking drugs is very effective in preventing ventricular arrhythmias in the long QT syndrome, although the response is genotype dependent (5, 71–74). The 10-year mortality rates among symptomatic patients decreased from approximately 50% in patients with the congenital long QT syndrome who were not treated to less than 5% after these patients were routinely prescribed β-blocker therapy (34, 35). A recent retrospective study by Moss and colleagues (70) among 869 patients with the congenital long QT syndrome revealed a statistically significant reduction in the rate of cardiac events in both probands and affected family members after initiation of β-blocker therapy. In patients with aborted cardiac arrest before β-blocker therapy, the probability of aborted cardiac arrest or sudden death was 6.6% when β-blockers were used (70). In patients with recurrent cardiac symptoms or aborted cardiac arrest, β-blocker therapy might not completely prevent sudden cardiac death, and implantable cardioverter defibrillator (ICD) therapy is warranted for these high-risk patients. An important criticism of this study is its retrospective nature and lack of evidence that patients continued to take their β-blockers. After it became clear that the congenital long QT syndrome is caused by ion channel mutations and not by imbalance of the cardiac autonomous nervous system, the rationale for performing left cardiac denervation has become less obvious.

Cardiac Pacing: Because the onset of torsade de pointes arrhythmias in patients with the congenital long QT syndrome has been associated with bradycardia or pauses during sinus rhythm (75–77), permanent cardiac pacing has been recommended as an adjuvant to β-blocker therapy in patients who also have bradycardia or atrioventricular conduction disturbances (78–83) or in carriers of *SCN5A* mutations, who usually have slow heart rates (84, 85). In addition, cardiac pacing can be an important adjuvant therapy in patients in whom β-blockers and left stellate ganglionectomy have proven inefficacious, even if bradycardia or conduction disturbances are not present (86).

Cardiac pacing should be aimed at preventing 1) bradycardia, by using a relatively high lower rate limit (≥80 beats/min), and 2) pauses, by using pause-prevention pacing algorithms, such as rate-smoothing. Viskin (84) reviewed applications of cardiac pacing.

Implantable Cardioverter Defibrillators: Implantable cardioverter defibrillators are increasingly being used to prevent sudden cardiac death (87, 88). Aborted sudden cardiac death and recurrent symptoms during combined β-blocker and pacemaker therapy are the most frequent indications for ICD implantation (87–89). Since the ICD does not alter the underlying substrate leading to arrhythmias, initiating or continuing β-blocker therapy is recommended (90).

Toward a Genotype-Specific Therapy for Symptomatic Patients: Clinical and experimental studies have recently supported the emerging sense that gene-specific therapy might be feasible for some forms of the congenital long QT syndrome. One of the first studies showed that patients with *LQT3* shorten their QT interval more in response to a Na^+ channel blocker (mexiletine) compared to patients with *LQT1* and *LQT2* (91). Because most patients with *LQT1* experience syncopal events during exercise, they should avoid competitive sports. As diving and swimming are particularly strong triggers for cardiac events in patients with *LQT1*, these activities should be strongly discouraged (37, 62, 92). Patients with *LQT2* should be advised to remove sources of loud noise from their direct environment (such as alarm clocks and telephones).

Patients with *LQT1* and *LQT2* genotypes typically benefit from β-blocker therapy (37, 70). Because the amplitude of I_{Kr} increases when extracellular potassium concentrations are increased (93, 94), researchers have attempted to increase K^+ levels in patients with *LQT2* by intravenously infusing potassium or administering the diuretic spironolactone (95). Indeed, QT intervals have been statistically significantly shortened in patients with *LQT2* (96) but also in patients with *LQT1* (97). Potassium supplementation is, however, hindered by difficulties in achieving sufficiently high K^+ concentrations with long-term oral therapy (98). On the other hand, nicorandil, a K^+ channel opener, has normalized repolarization abnormalities induced by epinephrine infusion in patients with *LQT1* (99).

A beneficial effect of β-blocker therapy has not been demonstrated for patients with *LQT3* (37, 70). Since patients with *LQT3* are at higher risk at slow heart rates, they may benefit from pacemaker therapy. Several clinical and experimental studies suggest a beneficial effect of Na^+ channel blockers, such as lidocaine–mexiletine (91, 100, 101), tocainide (100), or flecainide (85), in patients with *LQT3*, although long-term follow-up data are not available yet. However, flecainide may cause ECG changes reminiscent of the Brugada syndrome (familial idiopathic ventricular fibrillation) in many patients with *LQT3* (102). The Brugada syndrome is characterized by right bundle-branch block and ST-segment elevation in the right precordial leads on the ECG and may lead to ventricular fibrillation and sudden cardiac death (103). The effect of the flecainide-induced changes, which might suggest the introduction of a different arrhythmogenic substrate, is unknown. A further therapeutic differentiation based on the specific mutations in the affected gene can be expected in the near future.

Patients without Symptoms but with ECG Characteristics Suggestive of the Congenital Long QT Syndrome

Some individuals are not identified on the basis of their symptoms but because of typical electrocardiographic features suggestive of the congenital long QT syndrome. The principal diagnostic hallmark of the congenital long QT syndrome is lengthening of the QT interval on the 12-lead ECG. Because the QTc value is often not sufficiently long to make or exclude the diagnosis in borderline cases, Schwartz and colleagues (47) developed an elaborate point scoring system that goes beyond QTc duration (Table 1).

QT Prolongation

QT interval prolongation is usually most easily identified in leads II, V1, V3, or V5, but all 12 leads should be examined to identify the longest QT interval (104–106). Despite ongoing criticism, the Bazett correction formula ($QTc = QT/\sqrt{RR}$) for heart rate continues to be useful (41, 47, 104, 105). The cut-off value commonly used was a QTc interval of 440 ms or greater, but more recent genotype–phenotype correlations indicated that greater than 460 ms was more appropriate (37, 50). Indeed, 40% of carriers of *LQT1* and *LQT2* mutations show QTc values (410–470 ms) that overlap with those of noncarriers (36, 45). In this QTc range, phenotypic diagnosis from the ECG becomes imprecise and genetic studies help diagnose the congenital long QT syndrome. When a QTc of 460 ms or greater is used, the positive predictive accuracy for the congenital long QT syndrome is 96% in women and 91% in men; almost 100% positive predictive accuracy for the congenital long QT syndrome can be achieved at a QTc of 470 ms or greater in men and a QTc of 480 ms or greater in women (50). Finally, QTc intervals tend to be longer in patients with *LQT3* than in patients with *LQT1* and *LQT2* (36, 37, 45).

QT Interval Dispersion

The second ECG characteristic is QT interval dispersion, which can be measured as a lead-to-lead variability in QT intervals (107–109). It is debated whether this phenomenon reflects regional differences in ventricular repolarization times (110, 111). In normal individuals, the difference between maximum and minimal QT intervals measured on the standard resting ECG has varied between 48 ± 18 ms (104) and 54 ± 27 ms (112) (mean ± SD). In patients with the congenital long QT syndrome, however, regional dispersion of ventricular repolarization times has ranged from 93 ± 39 ms to 185 ± 26 ms (107, 108, 112, 113). In patients with the congenital long QT syndrome, QT dispersion may correlate with the risk for ventricular arrhythmias (107, 114), whereas a reduction in dispersion of the QT interval could be used as a marker of therapeutic efficacy (109).

T-Wave Structure

The congenital long QT syndrome alters not only the duration of repolarization (QT interval) but also its structure (115). The most typical presentation of the T wave may be biphasic (116) or notched (77, 116, 117) and is most prominent in the precordial leads (116, 117). In addition, T-wave alternans is an infrequently recorded highly arrhythmogenic ECG finding with transient beat-to-beat changes in amplitude, shape, and polarity of the T wave during sinus rhythm without concomitant QRS changes (118–120).

Bradycardia and Sinus Pauses

Signs of sinus node dysfunction, such as sinus bradycardia or sinus pauses (72, 121, 122), and lower-than-expected heart rate during exercise have been reported (35, 123–125). Slow heart rates are particularly striking in younger children (124). During submaximal exercise testing, many patients with the congenital long QT syndrome reach a heart rate lower than that achieved by healthy controls matched by sex and age (126, 127). Sinus pauses may play a role in the initiation of pause-dependent torsade de pointes arrhythmias (75, 76, 128). The congenital long QT syndrome might also be complicated by atrioventricular conduction disturbances, which are generally associated with poor prognosis (52, 83, 125).

Electrophysiologic Testing

Wellens and colleagues (129) performed one of the first comprehensive electrophysiologic studies in patients with the congenital long QT syndrome. The absence of inducibility by programmed stimulation indicates that the arrhythmias in the congenital long QT syndrome are probably not the result of reentrant circuits, but reentry probably plays a role in the perpetuation of torsade de pointes arrhythmias in the congenital long QT syndrome. It is therefore generally believed that electrophysiologic studies using one or more premature stimuli during ventricular pacing are of limited value in the diagnosis and treatment of patients with the congenital long QT syndrome (130, 131). On the other hand, torsade de pointes might be inducible using short-long-short sequences (76, 132). In addition, changes in heart rate provoked by, for example, the Valsalva maneuver or electrophysiologic protocols may lead to clear changes in the T-wave or ventricular tachycardia (77).

Response to Exercise

The standard resting ECG as a diagnostic criterion may misclassify members of families with the congenital long QT syndrome (50, 133, 134). Therefore, an exercise test might enhance diagnostic accuracy, because shortening of the QT interval was inadequate in patients with the congenital long QT syndrome (6, 67, 135–138). In addition, a submaximal heart rate response during exercise has been reported (52, 126, 136). Swan and colleagues (133) recently found a reduced maximum heart rate during exercise in patients with *LQT1* but a normal heart rate in patients with *LQT2*. During recovery from exercise, patients with *LQT1* showed an exaggeration of the QT interval prolongation compared with patients with *LQT2* (133). Finally, Schwartz and colleagues (91) reported that patients with *LQT3* display a higher degree of QT interval shortening in response to increase in heart rate than patients with *LQT2* (**Table 2**). Holter monitoring may also be useful (139), but well-defined criteria for QTc separation of the congenital long QT syndrome from normal patients are not available. Studies have demonstrated that QT intervals up to 500 ms occur in a substantial percentage of healthy individuals (140). Therefore, a QTc greater than 500 ms, particularly in association with T-wave abnormalities, would appear to be necessary to support the diagnosis of the congenital long QT syndrome (56).

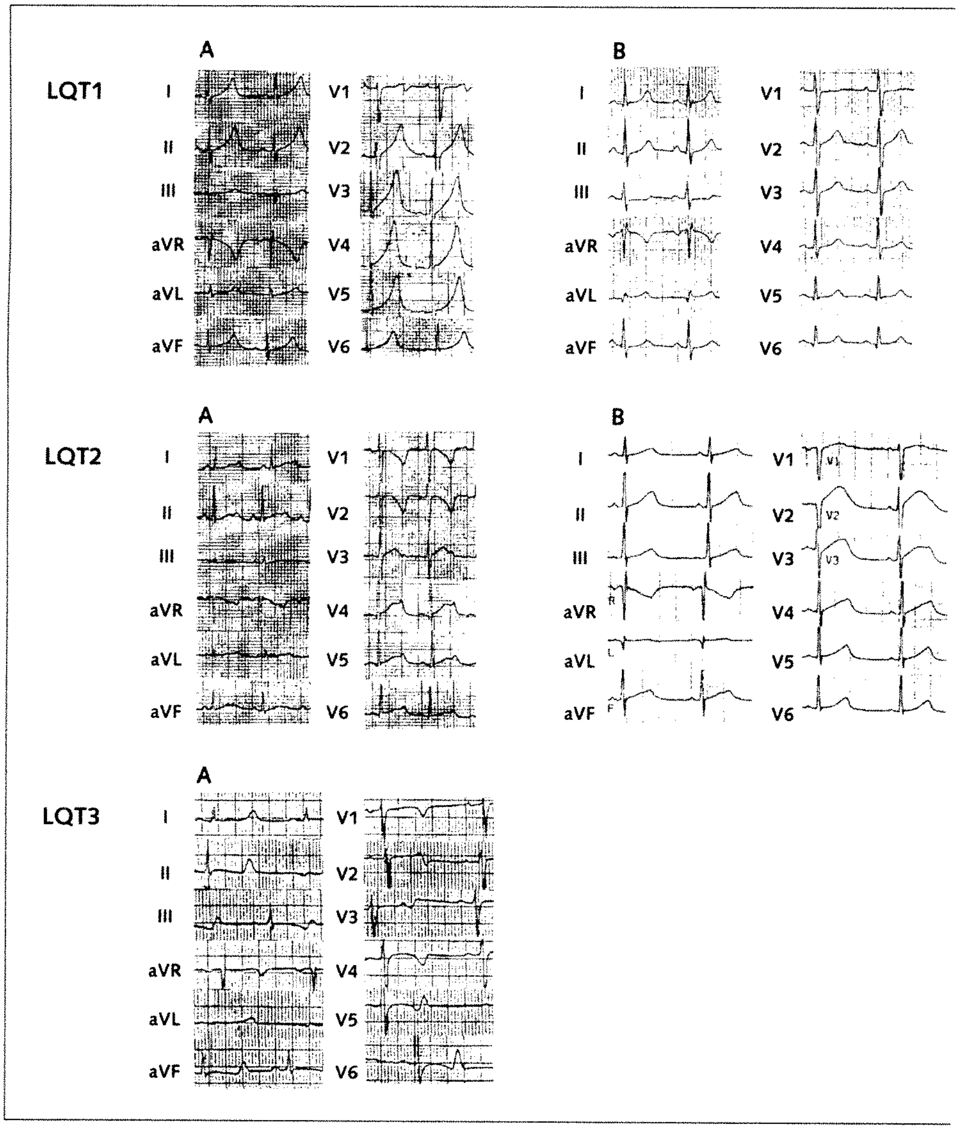
Genotype-Specific ECG Phenotypes in the Congenital Long QT Syndrome

The different time dependence and voltage dependence of the ionic currents involved in the congenital long QT syndrome are probably responsible for distinct ECG phenotypes that have been reported for the different genotypes. Initial studies by Moss and colleagues (36, 141) reported an association of certain T-wave patterns with *LQT1*, *LQT2*, and *LQT3*. Recently, Zhang and colleagues (142) recognized 10 typical ST-T wave patterns that are genotype-specific (4 *LQT1*, 4 *LQT2*, and 2 *LQT3*) (see **Figure 2** for the most important ECG patterns). These ECG characteristics, however, cannot be used to diagnose the type of congenital long QT syndrome but are useful for selecting which gene to investigate first when performing genetic analysis.

Treatment of Asymptomatic Patients with ECG Characteristics of the Congenital Long QT Syndrome

Treatment of asymptomatic patients is still controversial because most patients with the congenital long QT syndrome will never experience symptoms (36, 37) and sudden death during the first syncopal episode is unlikely (36). Schwartz (90) recommended that while waiting for more definitive data, physicians should begin treatment for only the following asymptomatic patients: those with congenital deafness; neonates and infants in the first year of life (because of the enhanced risk during the first months in

Figure 2. **Genotype-specific electrocardiographic (ECG) pattern in the congenital long QT syndrome.**



Top. The two most common *LQT1* ECG patterns: broad-based T-wave pattern (*A*) and normal-appearing T-wave pattern (*B*). **Middle.** The two most frequently encountered *LQT2* ECG manifestations: obvious bifid T waves (*A*) and subtle bifid T wave with a second component on top of the T wave in limb and left precordial leads (*B*) (or, alternatively, the second component on the downslope of T wave; not shown). **Bottom.** Most typical *LQT3* ECG pattern: late-onset peaked/biphasic T-wave (*A*). Modified from Zhang et al. Circulation. 2000;102:2849-55 (142), with permission.

life); siblings of children who have already died suddenly; patients with documented evidence of T-wave alternans; patients whose QTc exceeds 600 ms; and patients with manifest anxiety or patients explicitly requesting treatment.

Mutation Carriers without Symptoms or ECG Characteristics of the Congenital Long QT Syndrome

Approximately 10% of all mutation carriers have a normal QTc interval less than 440 ms (142). However, only 2% of all carriers of the congenital long QT syndrome mutation have a normal ST-T wave pattern with a normal QT interval. Priori and colleagues (143) showed that in some families, penetrance of clinical symptoms and QT interval prolongation may be as low as 25%. This implies that family members considered normal on clinical and ECG grounds could be silent gene carriers displaying a very mild phenotype (19). They would be unexpectedly at risk for generating affected offspring and perhaps also of developing torsade de pointes arrhythmias if exposed to either cardiac or noncardiac drugs that block potassium channels (9, 10). Molecular screening is therefore recommended in all family members of positively genotyped patients (21). Few patients with the congenital long QT syndrome without ECG abnormalities present with sudden death as their first symptom (105), although preliminary data suggest that sudden death can occur in silent gene carriers (144). Until more definitive data are available, con-

Table 3. **Drugs Reported To Provoke Ventricular Tachycardia in the Presence of a Specific Mutation in One of the Long QT Syndrome Genes**

Gene	Channel	Drug	Use	Reference
KCNQ1	I_{Ks}	Mefloquine	Antimalarial	147
KCNQ1	I_{Ks}	Disopyramide	Antiarrhythmic	147
KCNQ1	I_{Ks}	Terfenadine	Antihistamine	147
KCNQ1	I_{Ks}	Cisapride	Cholinergic antagonist	10
SCN5A	I_{Na}	Halofantrine	Antimalarial	148
MiRP1	I_{Kr}	Clarithromycin	Antibiotic	16
MiRP1	I_{Kr}	Quinidine	Antiarrhythmic	9
MiRP1	I_{Kr}	Sulfamethoxazole	Antibiotic	9
MiRP1	I_{Kr}	Procainamide	Antiarrhythmic	9
MiRP1	I_{Kr}	Oxatomide	Antihistamine	9

servative management of silent gene carriers seems reasonable because the value of β-blocker therapy in this group of patients is still unknown.

Patients Carrying Mutations or Polymorphisms Associated with Drug-Provoked Long QT Syndrome

Some patients carry a predisposition for drug-induced torsade de pointes arrhythmias on the basis of the congenital long QT syndrome–related ion channel mutations (7, 97, 145). These patients are usually clinically asymptomatic until administration of a drug. A genetic predisposition to drug-provoked long QT syndrome torsade de pointes can be caused by mutations in the *KCNE2* subunit of the I_{Kr} potassium channel (16, 146) or a mutation in the *KCNQ1* subunit of the I_{Ks} channel (10, 147) (**Table 3**). In addition, a polymorphism in the *KCNE1* gene (148), as well as two relatively common polymorphisms in *KCNE2* (allelic frequency in both cases around 1.6%), has been associated with quinidine- and erythromycin-induced long QT syndrome (9, 16). Drug-provoked long QT syndrome has also been linked to a mutation in *SCN5A* (149). In 34 patients with drug-induced long QT syndrome, we detected two previously described mutations in ion channels. None of the additional polymorphisms resulted in amino acid changes in ion channel proteins (Doevendans and colleagues. Personal communication).

However, in most patients with the acquired long QT syndrome (>85%), no ion channel mutations have been identified thus far. In this case, the acquired long QT syndrome is thought to result from electrolyte disturbances; hypertrophy; or treatment with commonly used medications, including some antiarrhythmic, antihistamine, antibiotic, psychoactive, and gastrointestinal prokinetic agents (150). In patients without ion channel mutations, proarrhythmia is probably induced by block of the potassium current I_{Kr} (151). Recent studies have clarified why so many structurally diverse compounds block *KCNH2* channels but not other potassium channels. Because the *KCNH2* channel has a unique group of amino acids in the S6 domain that are not present in other voltage-gated K^+ channels (*Kv1* to *Kv4*), many drugs preferentially block *KCNH2* channels (9), placing patients at risk for cardiac arrhythmias. The acquired long QT syndrome occurs more often in females (152).

Genetic diagnostic approaches in patients with the acquired long QT syndrome should be restricted to centers with sufficient experience in the genetic identification of these patients. The relevance of the polymorphisms is not clear yet, and there is no well-defined set of genes that have to be analyzed. A pragmatic approach is to provide a list of compounds that should not be used in the future and should be known to both mutation carriers and patients with the congenital long QT syndrome.

SUMMARY

The congenital long QT syndrome is a potentially life-threatening condition characterized clinically by prolonged QT intervals, syncope, and sudden cardiac death. The abnormally prolonged repolarization is the result of mutations in genes encoding cardiac ion channels. The diagnosis of the congenital long QT syndrome is based on clinical, ECG, and genetic criteria. β-Blocker therapy is important in the treatment of the congenital long QT syndrome, although pacemakers and ICDs are useful for some patients. In the near future, mutation-specific treatment will probably become a novel approach to this potentially fatal syndrome.

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Smallpox Manifestations and Survival during the Boston Epidemic of 1901 to 1903

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Clinical records of 243 patients with smallpox consecutively admitted to the Southampton Street smallpox hospital in Boston, Massachusetts, during the 1901–1903 epidemic were reviewed. Smallpox was divided into five categories of varying severity; 47% of patients had varioloid, a relatively mild form of the disease usually occurring in previously vaccinated individuals with incomplete immunity. Survival information is available for 206 patients, of whom 36 (17.5%) died. Vaccination status, disease severity, and age were associated with survival, whereas sex, birthplace, and race were not. While full recovery often took weeks, most deaths occurred 7 to 14 days after the onset of symptoms, and all deaths occurred within 18 days of symptom onset. Smallpox was eradicated worldwide in 1977, but knowledge of the disease is essential because its cause, variola virus, is considered a potential biological weapon.

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A smallpox epidemic occurred in Boston, Massachusetts, from 1901 to 1903, with a total of 1596 reported cases and 270 deaths (17%) (1). Although more than 95% of reported smallpox cases in the United States during the 20th century—including over 200 000 cases in 1920 to 1921—were caused by a mild variety of the disease, variola minor, the Boston epidemic was caused by the classic variola major form (2, 3). The cutaneous manifestations caused by variola minor and variola major are similar; however, patients with variola minor have slightly smaller lesions that evolve more rapidly, do not usually become seriously ill, and have a mortality rate less than 1% (2, 3). Naturally occurring smallpox was eradicated in 1977, but awareness of the disease must be maintained because variola virus remains a potential bioterrorism agent (4–6). We describe clinical manifestations of smallpox during Boston's last major epidemic and analyze factors associated with survival among patients admitted to one hospital.

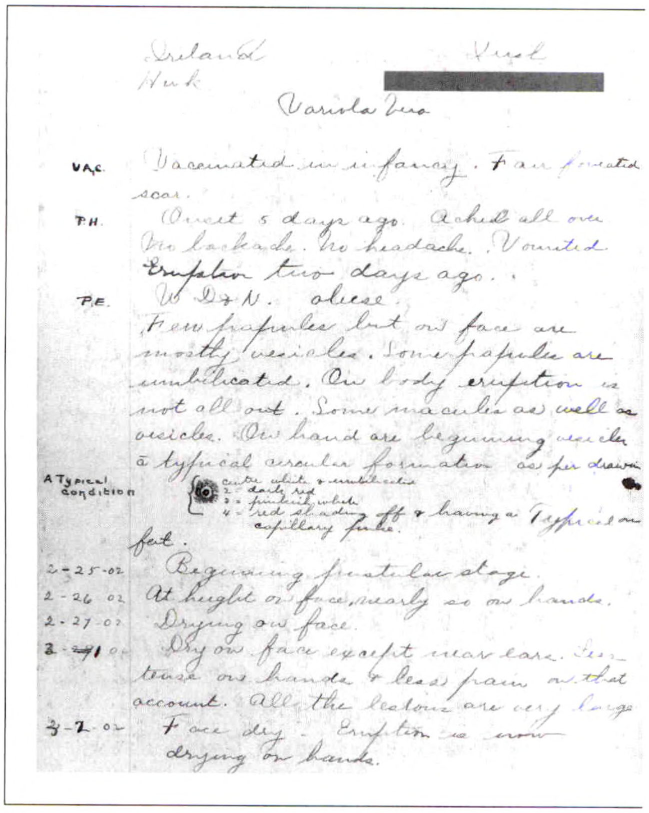
BACKGROUND

Because few physicians today have seen a case of smallpox, a summary of its clinical course is warranted. Smallpox is usually spread person-to-person in virus-laden droplets expelled from the oropharynx. The infection begins with seeding of the virus in the upper respiratory tract and regional lymph nodes, followed by involvement of the skin and internal organs (3, 7, 8). After a 7- to 17-day incubation period (mean, 10 to 12 days), clinical onset begins with a 3-day pre-eruptive stage that most commonly includes fever, malaise, headache, and backache. The exanthem generally starts on the face and spreads over the body in a centrifugal distribution, with greater involvement of the face and extremities than the trunk. A hallmark of the smallpox rash is its monomorphic appearance, with lesions appearing essentially as a single "crop" and evolving together through different stages as erythematous macules, papules, vesicles, pustules, and crusts. Vesicles often develop a central umbilication that persists into the pustular stage. The enanthem of smallpox appears as erythematous macules that evolve into papules and vesicles and may involve the oropharynx, tongue, and nasal cavity. The rash resolves over 14 to 21 days, leaving disfiguring, pitted scars (with a predilection for the face) in more than half of typical cases of variola major. Complications of smallpox include encephalitis, pneumonitis, pneumonia, secondary cutaneous infection, arthritis, conjunctivitis, keratitis, and corneal ulceration (which can lead to blindness).

DETENTION OF PATIENTS WITH SMALLPOX DURING THE EPIDEMIC

All patients with smallpox in Boston during the epidemic, except those considered too sick to be moved from their homes, were detained at the Southampton Street or Gallop's Island hospitals, which were operated by the city of Boston (9–11). The Southampton Street smallpox hospital served as the major smallpox isolation and treatment facility. The Gallop's Island quarantine facilities, in Boston Harbor, were hastily expanded when additional beds were needed in the fall of 1901. Beginning in November 1901, a portion of men with smallpox were sent to Gallop's Island, either directly or by transfer from the Southampton Street hospital, if they "could be moved with safety" (9). Removal to Gallop's Island was historically objected to by many Bostonians because they associated Gallop's Island with neighboring penal institutions (12). Female and pediatric patients were treated at the Southampton Street smallpox hospital; however, one woman in this study was transferred to Gallop's Island with her husband. In 1902, 925 patients with smallpox were admitted to the Southampton Street smallpox hospital, with 142 of these subsequently transferred to Gallop's Island; 94 patients were directly admitted to Gallop's Island; and 5 patients remained at their homes (10). Milder cases tended to be sent to Gallop's Island. In 1902, the mortality rate was 11% at Gallop's Island compared with 20% at the Southampton Street smallpox hospital (10). Patients with smallpox were strictly excluded from all other hospitals in the city; early in the epidemic, the Boston City Hospital

Figure 1. **An example of clinical notes.**



Ireland [illegible]
[illegible] [redacted]

Variola Vera

VAC. Vaccinated in infancy. Fair foveated scar.

P.H. Onset 5 days ago. Ached all over. No backache. No headache. Vomited. Eruption two days ago.

P.E. W D & N. obese.
Few papules but on face are mostly vesicles. Some papules are umbilicated. On body eruption is not all out. Some macules as well as vesicles. On hand are beginning vesicles ā typical circular formation as per drawing

A Typical condition
centre white & umbilicated
2 = dark red
3 = pinkish white
4 = red shading off & having a typical capillary fringe.
Typical on feet.

2-25-02 Beginning pustular stage.
2-26-02 At height on face, nearly so on hands.
2-27-02 Drying on face.
3-~~2~~1-02 Dry on face except near ears. Less tense on hands & less pain on that account. All the lesions are very large
3-2-02 Face dry. Eruption is now drying on hands.

Clinical records were compiled in a single, bound book. Demographic information, smallpox type, and vaccination history were recorded at the beginning of a patient's record (name, age, and marital status are not shown but were listed at the top of the page). The patient was a 43-year-old woman who was discharged "well" on 22 March 1902. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

was temporarily quarantined when two inpatients developed the disease (13).

METHODS

Patient Records

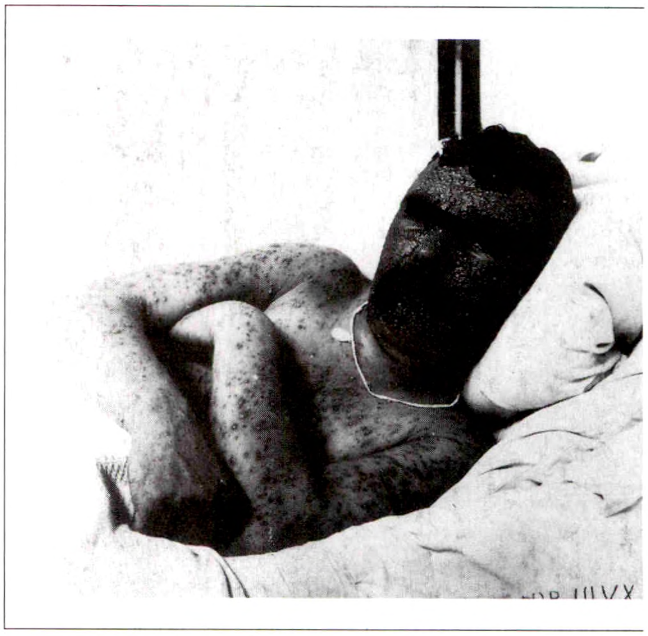
We reviewed clinical records of 243 patients with smallpox from the Boston epidemic. These patients were consecutively admitted to the Southampton Street smallpox hospital from 23 January to 3 April 1902. The medical records, recorded by Dr. Irving Reed Bancroft (1872–1963), are the only known existing records from the epidemic (**Figure 1**) (14). Dr. Bancroft, a 1900 graduate of Harvard Medical School, trained as the resident physician at the Southampton Street hospital during the epidemic, and he continued in a career in dermatology after the epidemic (15, 16). Records were obtained from the Boston Medical Library in the Francis A. Countway Library of Medicine, Boston, where they were donated in 1974. We excluded patients who did not have smallpox but were admitted for quarantine because of exposure and one patient who after admission was determined to have generalized vaccinia.

Statistical Analysis

The primary end point was survival duration, calculated as the number of days from onset of symptoms until discharge alive or death. The probability of survival was calculated by using the Kaplan–Meier method; survival curves were stratified by the following variables: type of vaccination ("successful," "unsuccessful," "recent 'primary'," or "none"), disease severity, sex, age, race, or birthplace. In most instances, the confidence intervals for survival probabilities at various time points were computed by using the Rothman method (17). When there were no failures in a subgroup of patients, the exact binomial confidence was formed about 100%, based on the number remaining at risk at that time point. Patients who were discharged alive were treated as censored observations after the date of their last evaluation. The log-rank test for homogeneity among strata was used, with *P* values unadjusted for multiple comparisons.

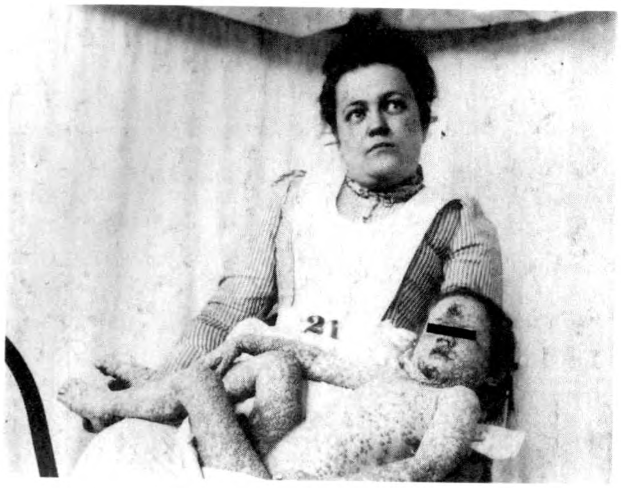
Vaccination was interpreted as "successful" if it had been administered more than 3 weeks before admission and evidence of a scar or "take" was described; an "unsuccessful" vaccination left no scar; and "none" refers to patients with no history of vaccination. Patients with a "recent 'primary'" vaccination had no history of successful vaccination but were vaccinated within 3 weeks of admission. These patients were considered separately because they were likely infected at the time of their vaccination. Disease severity was defined as "mild" for varioloid cases, "intermediate" for variola vera cases, and "severe" for hem-

Figure 2. **Day 7 of the varioloid form of smallpox in a 34-year-old man.**



The patient had been successfully vaccinated in infancy and was discharged "well" 2 weeks later. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

Figure 3. **Day 8 of variola vera in a 3.5-year-old girl with an unidentified nurse at the Southampton Street smallpox hospital.**


[redacted]

The patient had been unsuccessfully vaccinated 3 months before admission. Pustules appear in the same stage (monomorphic)—a characteristic feature of smallpox. She was discharged "well" 1 month later, although facial pitting was noted. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

orrhagic disease. Race was considered black or nonblack. Birthplace was categorized as United States, Europe, or Canada (only two patients were categorized as "other" and were excluded from analyses involving birthplace). Thirty-three patients who were transferred to Gallop's Island were excluded from survival analyses since all were transferred within 48 hours of admission and the outcome of their disease is unknown. In addition, one patient who died after secondary infection of her vaccination site (that is, not from smallpox) was excluded from smallpox survival analyses.

After univariate analysis (Kaplan–Meier curves with a log-rank test evaluation), Cox proportional hazards models (18) were constructed to determine which covariates were important with respect to survival when considered jointly. A likelihood ratio test was also performed to identify whether type of vaccination or disease severity were important factors in survival after adjustment for demographic characteristics identified as having potential importance. Statistical analyses were performed by using SAS software, version 8 (SAS Institute, Inc., Cary, North Carolina). All reported *P* values are two sided.

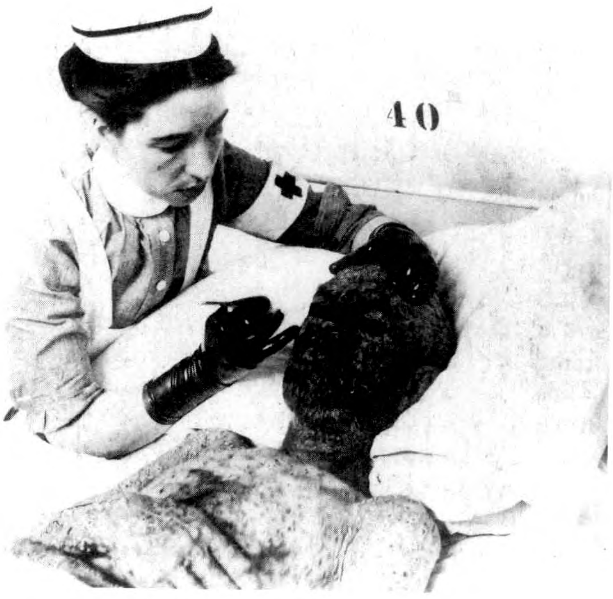
CLINICAL PRESENTATION

At the time of the epidemic, the standard practice was to divide cases into five clinical categories. *Varioloid*, or mild disease, usually occurred in patients with a history of successful vaccination that modified the clinical course (**Figure 2**). *Variola vera* was typical smallpox (**Figures 3** to 5), and the severe hemorrhagic forms—*variola pustulosa hemorrhagica* and *purpura variolosa*—were marked by purpura. The two hemorrhagic forms were distinguished by whether the purpura preceded (purpura variolosa) or followed (variola pustulosa hemorrhagica) the skin eruption. *Variola sine eruptione* was defined as constitutional symptoms with few or no skin lesions (19).

Of 230 patients for whom the form of smallpox was listed, 109 had varioloid disease, 117 had variola vera, 3 had variola pustulosa hemorrhagica, and 1 had purpura variolosa. No patients were admitted with the diagnosis of variola sine eruptione. Eleven patients (7 with varioloid and 4 with variola vera) who had recently been vaccinated were given a concomitant diagnosis of "vaccinia," a designation that appears to have included patients with smallpox who had only a localized reaction to the vaccinia vaccine.

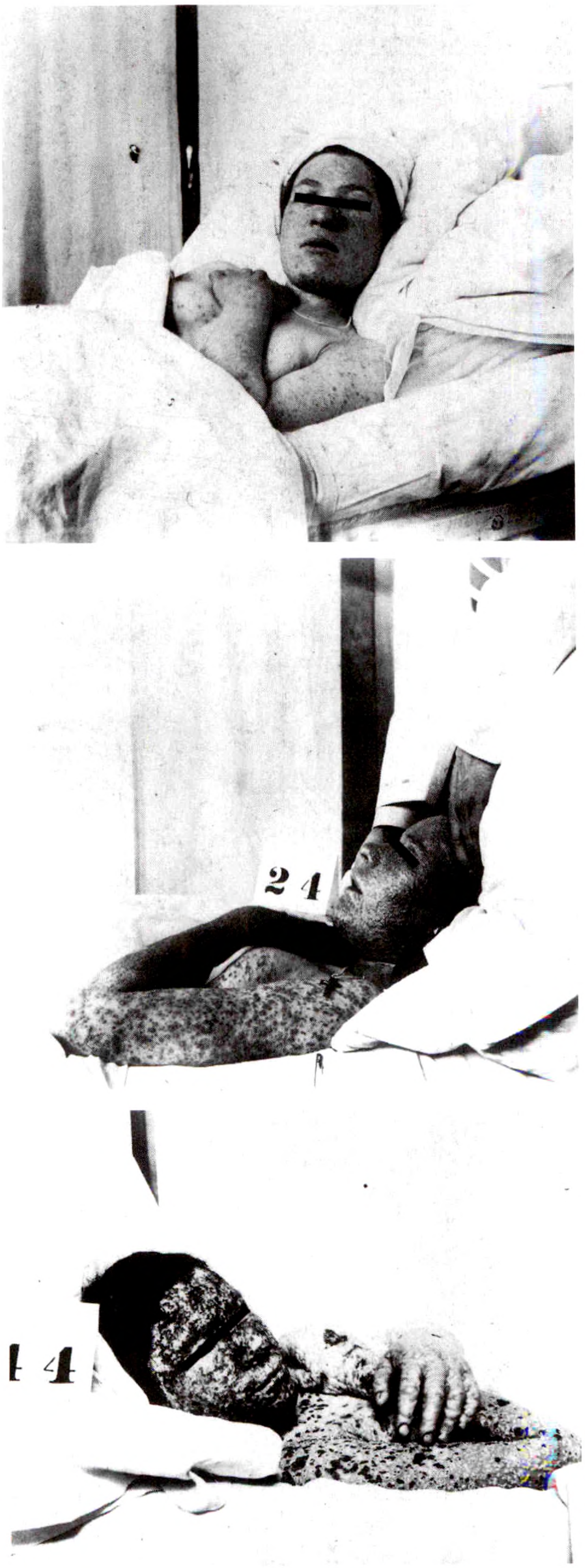
Patients with varioloid at the Southampton Street smallpox hospital were described as having fewer and smaller or "aborted" lesions. A 27-year-old woman with a mild case of varioloid was described: "Very light papular eruption. Fifteen–twenty [lesions] only on face and less severe on body . . . No constitutional disturbances or temperature" (14). A 2.5-year-old girl with variola vera, who had been unsuccessfully vaccinated 2 months earlier, was

Figure 4. **An unidentified nurse cleaning the eyes of a delirious 45-year-old man with variola vera (date of onset uncertain).**



The patient had a history of successful vaccination in infancy. On discharge 1 month later, he was described as "well": "weak on legs but is apparently mentally sound . . . has one discharging boil on legs." (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

Figure 5. **A 23-year-old unvaccinated woman with variola vera.**



The patient at day 4 (*top*), day 6 (*middle*), and day 11 (*bottom*) after the onset of illness. There appear to be purpuric lesions on days 6 and 11. A diagnosis of a hemorrhagic form of smallpox had been considered by staff shortly after admission. The patient died on day 12. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

described at the time of admission as follows: "Eruption is severe and prostration is great. Eruption is now in late papular stage and is nearly confluent on face. Is sparse on body especially on abdomen and is thicker on legs but still not entirely confluent" (14). Two days later the rash had evolved: "Eruption is vesicular and early pustular. [Skin] [i]s broken down and is excoriated in many places." Four days after admission, and 1 day before the patient died, Bancroft wrote: "Pustular and crusted on face. Face is swollen and eyes are closed. Pulse and temperature rising" (14).

Subsequent classification systems would be proposed for smallpox (3, 7). The classification system listed by the World Health Organization in 1988 divided the disease into five types: hemorrhagic (early and late forms), ordinary, modified, flat, and variola sine eruptione. This was similar to the classification system used at the time of the epidemic, the main difference being the inclusion of the severe flat type of the disease, postulated to reflect a deficient cellular immune response to the virus.

Complications described in the clinical notes included sepsis, lobar pneumonia, sublingual abscess, parotitis, conjunctivitis, iritis, keratitis, "septic" extremities or joints, skin abscesses, furunculosis, and "septic scales" (impetigo). After vaccination at the hospital, a newborn patient developed a "septic arm" that caused death. Documented laboratory abnormalities included albuminuria and leukocytosis; at times, the leukocyte count exceeded 30 000 cells/mm^3.

RESULTS

Although we reviewed records from 243 consecutive patients, detailed information on individual characteristics was available in varying numbers of patients (**Table 1**). Sixty percent of patients were male, and the median patient age was 30 years. Blacks and immigrants made up 7% and 47% of the patient population, respectively. Seventy-three percent of patients had a history of vaccination before admission. The type of vaccination was determined for 234 patients, and 123 (53%) had evidence of successful vaccination. The type of vaccination and disease severity were indicated for 222 patients. Vaccination was successful in 84 of 105 (80%) varioloid cases, 32 of 113 (28%) variola vera cases, and 1 of 4 (25%) hemorrhagic cases. A history of vaccination and scar at the site were considered to represent successful vaccination; however, scars may have been acquired many years previously, with resultant diminished immunity.

Of 239 patients for whom discharge information was listed, 169 patients (71%) had recovered at discharge, 36 patients died (15%), and 33 adult patients (14%) were transferred to Gallop's Island within 48 hours of admission. All but 1 of the transferred patients were male, and they tended to have milder disease—19 of 26 (73%) were classified as varioloid and 7 of 26 (27%) as variola vera. One other patient, a 4-year-old boy who developed a "septic elbow joint" during his illness, was discharged with this condition at the request of his parents.

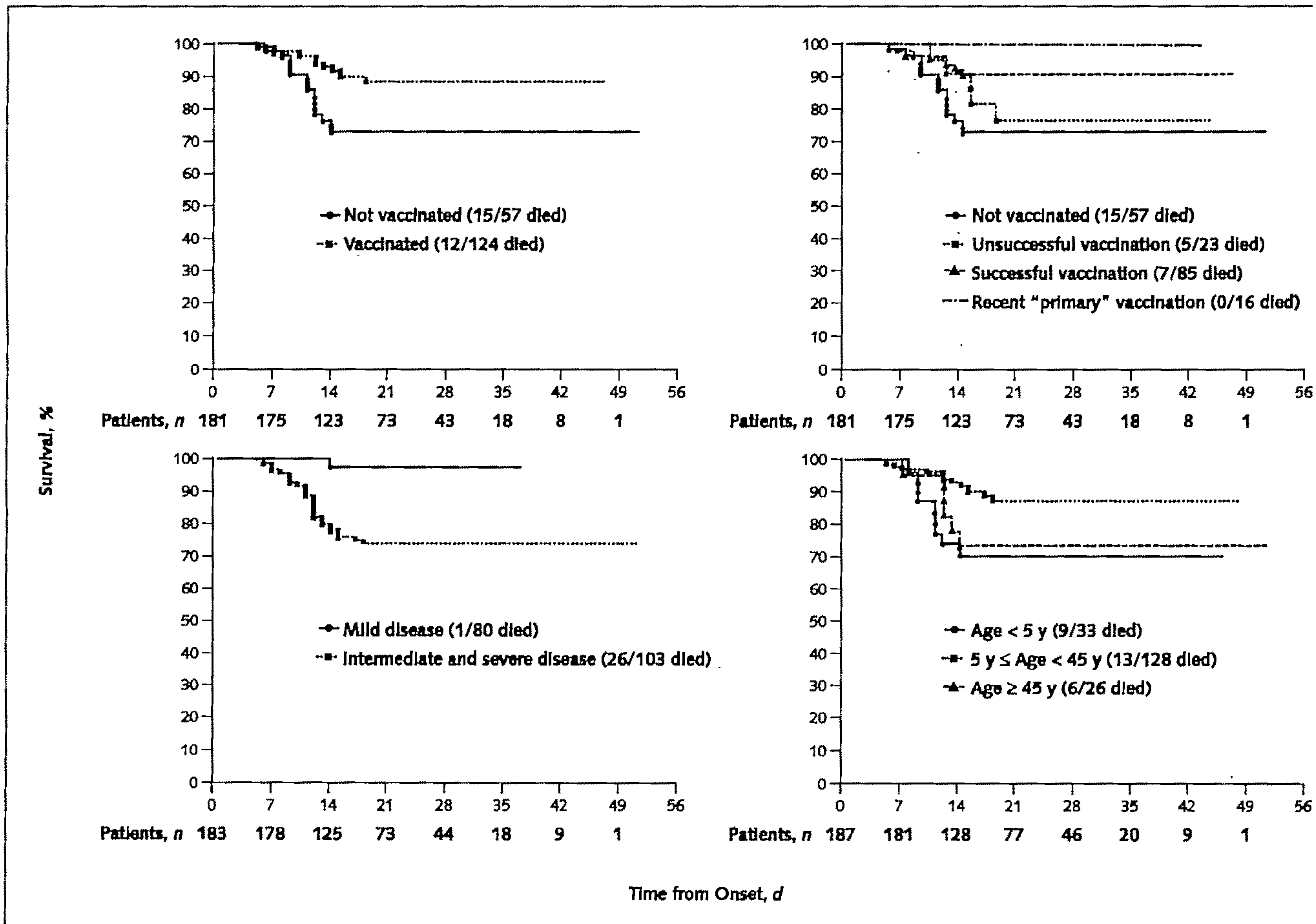
We performed survival analysis for nontransferred patients. Survival time was calculated from the date of symptom onset instead of the admission date because the former was considered a better reflection of the natural history of the disease; we excluded 17 patients whose time of symptom onset was not listed or was uncertain. These patients had a smaller 2-week probability of survival (55%) beginning from the date of admission than did all patients with or without information about symptom onset (81%). However, because the fraction of total patients who lacked onset information is small, overall actuarial survival at 2 weeks starting at admission only changed from 81% to 83% by their exclusion. Furthermore, no significant association was found between the presence or absence of onset information and sex, birthplace, race, type of vaccination, disease severity, or age.

Table 1. **Studied Variables and Number of Patients with Available Data (243 Total Patients)**

Variable	Patients, *n*
Admission date	242
Sex	240
Age	240
Discharge status	239
Birthplace	238
Race	238
Discharge date	238
Disease severity	230
Date of symptom onset	222

For the 188 patients with information on onset date and discharge status reported, the actuarial survival proba-

Figure 6. **Survival of patients with smallpox from date of symptom onset.**



Survival stratified by vaccination status ($P = 0.005$) (*top left*); type of vaccination (global $P = 0.012$; $P = 0.005$ for successful vs. none; $P = 0.034$ for recent primary vs. none) (*top right*); disease severity ($P < 0.001$) (*bottom left*); and age (global $P = 0.015$; $P = 0.008$ for patients younger than 5 years of age vs. patients 5 years of age or older and younger than 45 years of age; $P = 0.048$ for patients 45 years of age or older vs. patients 5 years of age or older and younger than 45 years of age) (*bottom right*). Symbols indicate deaths, and the numbers of patients at risk are indicated at 7-day intervals along the x-axis.

Table 2. **Survival Probabilities at 14 and 21 Days from Disease Onset**

Variable	Value	14-Day Survival Probability (95% CI), %	21-Day Survival Probability (95% CI), %	Overall P Value
Vaccination status	None	73 (60–83)	73 (60–83)	0.005
	Yes	92 (86–96)	89 (81–94)	
Vaccination type	None	73 (60–83)	73 (60–83)	0.012
	Unsuccessful	91 (73–98)	77 (56–90)	
	Successful	91 (83–96)	91 (83–96)	
	Recent "primary"	100 (75–100)	100 (72–100)	
Disease severity	Mild	98 (91–100)	98 (91–100)	<0.001
	Intermediate and severe	78 (70–85)	75 (65–82)	
Age	Age < 5 y	71 (54–84)	71 (54–84)	0.015
	Age ≥ 5 y and < 45 y	93 (87–96)	88 (81–93)	
	Age ≥ 45 y	74 (53–87)	74 (53–87)	

bility at 20 days was 84%. Seventy-nine percent of deaths occurred 7 to 14 days after the onset of symptoms, and all deaths occurred within 18 days. Patients with a history of vaccination had a higher probability of survival than patients who were not vaccinated (**Figure 6**, *top left*). At 14 days from symptom onset, the probability of survival for the group with vaccination was 92% (95% CI, 86% to 96%) compared with 73% (CI, 60% to 83%) for the patients who were not vaccinated. When vaccinated patients were further stratified by type of vaccination, those with successful vaccination or recent primary vaccination had a significantly higher probability of survival than those with no vaccination (**Figure 6**, *top right*). The probability of survival decreased with increasing disease severity (**Figure 6**, *bottom left*); only 1 of the 80 patients with complete data given a diagnosis of varioloid died. Patients younger than 5 years of age or 45 years of age or older had a lower probability of survival than patients in the middle age group (≥5 years and <45 years) (**Figure 6**, *bottom right*). **Table 2** summarizes the 14- and 21-day survival probabilities and overall P values based on the variables of vaccination status, disease severity, and age. Survival was not statistically significantly associated with sex, birthplace, or race.

To assess the simultaneous importance of factors identified as being potentially prognostic by univariate analyses, we performed a stepwise Cox proportional hazards analysis. The following covariates were included in the analysis: vaccination status, disease severity, and age. The resulting model contained both disease severity and age as covariates (with age <5 years and ≥45 years as higher-risk categories) (**Table 3**, *model 1*). A likelihood ratio test revealed that disease severity was significantly associated with survival after adjustment for age. A competing model containing vaccination status and age is also included in **Table 3**, model 2.

Table 3. **Results of Cox Proportional Hazards Model Analysis**

Model	Variable	Hazard Ratio (95% CI)	P Value
1	Disease severity (intermediate and severe vs. mild)*	17.13 (2.30–127.43)	0.005
	Age (<5 y vs. ≥5 y)	2.57 (1.08–6.12)	0.034
	Age (≥45 y vs. <45 y)	2.90 (1.09–7.74)	0.033
2	Vaccination status (no vs. yes)	3.20 (1.48–6.95)	0.003
	Age (≥45 y vs. <45 y)	2.64 (1.05–6.67)	0.040

* $P < 0.001$ for likelihood ratio test relative to age.

DISCUSSION

Analysis of clinical notes from the Boston smallpox epidemic of 1901 to 1903 reveals the broad variation in disease severity. Our study describes the effect that previous vaccination had on clinical presentation and survival. Patients with a history of vaccination were more likely to develop the relatively mild varioloid form of disease and had a higher probability of survival compared with patients who were not vaccinated. This suggests that while these patients had incomplete immunity and were susceptible to infection, vaccination could protect them somewhat by modifying disease severity. Also of interest are patients with a history of recent primary vaccination. These patients, who had no history of successful vaccination but had been vaccinated within 3 weeks of admission, had an increased probability of survival compared with patients who had never been vaccinated. Because vaccinia inoculated into the arm has a shorter incubation period (6 to 8 days) than variola virus acquired through respiratory inhalation, vaccination can alleviate or even abort smallpox if given soon after exposure (3, 20).

Age and disease severity were also associated with survival in our study. Infants and older patients were vulnerable to death from smallpox; patients younger than 5 years of age or 45 years of age or older had a lower probability of survival than those 5 years of age or older and younger than 45 years of age. Not surprisingly, disease severity was also associated with survival; patients with varioloid smallpox did better than those with variola vera or hemorrhagic disease.

Although analysis of a historical cohort from the Boston epidemic is informative, our study has obvious limitations. The historical clinical notes seem to have been recorded consistently; however, this was not a controlled study, and we cannot be sure that the data do not contain potential sources of bias of which we are unaware. In addition, no information is available on the ultimate survival status after patients were discharged from the hospital alive. Patient records were available for only a portion of those who contracted smallpox in the epidemic. A larger study group might have indicated additional or different predictors of survival. Complete data were available for most but not all patients studied, and we had to exclude from survival analyses 33 adult patients (32 of whom were male) who were sent to Gallop's Island within 48 hours of admission. Transferred patients probably had a lower mortality rate than nontransferred patients since they tended to have varioloid cases; however, their outcomes are unknown.

The major concern about smallpox today is its possible reappearance as a biological weapon. Management at present would involve many of the same approaches used 100 years ago: reporting to local and national health authorities; isolation; treatment of symptoms and signs; and selective vaccination of patients and their contacts, medical staff, and the community. Specific treatment recommendations for patients with smallpox include strict respiratory and contact isolation, vaccination during the incubation period, maintenance of adequate nutrition and hydration, and systemic antibiotic therapy for secondary bacterial infection (21). The cytosine nucleotide analogue, cidofovir, approved for treating cytomegalovirus retinitis in AIDS, has been proposed as a potential therapeutic agent for smallpox. Because the threat of the deliberate release of variola virus is considered low, preexposure mass vaccination is not considered advisable (21). Adverse effects that may result from vaccination include autoinoculation, ocular vaccinia, generalized vaccinia, severe progressive vaccinia, erythema multiforme, eczema vaccinatum, and postvaccinial encephalitis. Immunosuppressed persons are at particular risk for severe complications.

How would a smallpox epidemic today compare with that in Boston in 1901 to 1903? Clearly, many advantages in managing a smallpox epidemic exist today compared to a century ago. In addition to obvious therapeutic advances in supportive care and treatment of secondary bacterial infection, we have the benefits of regulation of vaccine production and quality, a more developed state and national public health infrastructure, greater federal support, and the experience of the World Health Organization's global Smallpox Eradication Program of the 1960s and 1970s. One hopes that there would be greater regard for civil liberties and ethical considerations than occurred during the Boston epidemic (1).

On the downside, we would share some of the same problems faced in the 1901–1903 epidemic. The lack of familiarity with smallpox among physicians is a concern, which was true in Boston in 1901 (22). Of greater importance is the fact that today most populations are unvacc nated and, thus, would be susceptible to infection. Sim larly, when the Boston epidemic began, "the larger portio of the people were in a receptive condition for the disease, and 485 000 vaccinations were administered (mostly b family physicians and private agencies) by the end of 1901 (9

Unlike 100 years ago, cases of smallpox are a hypc thetical concern for us at present. Nonetheless, the threa of variola virus as a potential bioterrorism agent is lessene by preparedness, including emergency guidelines from th Centers for Disease Control and Prevention; continue awareness of the disease by clinicians; the availability (large stocks of vaccine virus for use in the event of a outbreak; and ongoing research into antiviral drugs, nov vaccines, and tests for early diagnosis (20).

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AD LIBITUM

Geode

A crisp sheet, empty. Your pillow puffed
without its depression—I've come in time
to miss seeing my friend this morning
and with a bit of luck when you get back
from radiation, you'll fall so soundly
asleep, I'll miss you again this afternoon.

Just look at the clutter on your table—
that black comb you rivet compulsively
through what's left of your hair, a box of taffy
from the office, a book about Major
John Wesley Powell and a Mexican geode,
sliced in half. *What a loser the man is!*

The tinny voice of your niece, confessing
she's had it; she won't visit your room
until hell freezes over, not since you tossed
her husband out. *Jealous, that's what he is,*
the old fart. Your geode, intractably dull
on the outside, holds a cracked beauty within.

What am I doing, poking around in this?
I can't remember the last time I stopped
and held a rock to the light, no audience—
the luminous quartz peaks, they transform
the rest of it—your chipped comb, the book,
my brilliant morning. I'm glad you're gone.

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EDITORIAL

Echinacea for the Common Cold: Can Alternative Medicine Be Evidence-Based Medicine?

Echinacea, a plant indigenous to the midwestern United States, was first used for medicinal purposes by Native Americans. By the end of the 19th century, echinacea was employed as a treatment for a variety of ailments, including the common cold. During the 20th century, U.S. interest in echinacea waned, but this remedy became popular in Europe, especially Germany. The Dietary Supplement Health and Education Act of 1994 removed much of the regulatory oversight from the marketing and sale of herbal remedies and has resulted in renewed interest in echinacea as a common cold treatment in the United States. Despite the long history and current popularity of echinacea as a common cold remedy, the scientific evidence of its efficacy is unconvincing. Studies of various echinacea preparations have reported beneficial effects on the common cold, but methodologic flaws have limited acceptance of these results (1).

The study by Barrett and colleagues in this issue (2) is a valuable contribution to the literature on echinacea because it addresses many of the shortcomings of earlier studies. Barrett and colleagues assessed the effect of echinacea on the severity and duration of common cold symptoms in a sample of young adults with naturally acquired colds. No effect of echinacea was demonstrated on the overall course and severity of colds or on the severity of individual symptoms. The study had sufficient power to detect a 22% reduction in severity of symptoms, similar to the treatment effect of antihistamines on rhinorrhea or oral adrenergic agents on nasal obstruction. Although this study was carefully done and the results are clear, Barrett and colleagues correctly state that their work will not end the discussion about the efficacy of echinacea for the common cold.

One obstacle to the performance of definitive studies on this issue is the fact that different medicinal preparations of echinacea have different compositions. Three different species of echinacea, each with a different phytochemical composition, are used for medicinal purposes. In addition to the selection of plant species, the composition of the final product may be altered by the part of the plant used, the method of extraction, and even the season in which the plant is harvested. As a result of these effects, variability in phytochemical composition has been described not only among different echinacea preparations but also between lots of the same product (3). It has been suggested that different preparations of echinacea be standardized by measuring specific components, as Barrett and colleagues did. However, given the many variables that influence the composition of the preparations, it may be difficult to reproduce the material used in a particular study even when this information is provided.

Another obstacle to a systematic approach to the study of echinacea is that neither its "active" component nor its mechanism of action for treatment of cold have been defined. Several constituents of echinacea have been evaluated and shown to have various biological effects. The relevance of the reported effects to common cold pathogenesis, however, is not obvious. Extracts of echinacea have been reported to have antiviral activity, but there are no reports of antiviral effects on viral respiratory pathogens (4–8). As noted by Barrett and colleagues, the putative benefit of echinacea for treatment of respiratory infections is frequently attributed to the immunostimulatory properties of the various constituents (9). A growing body of literature, however, suggests that the symptoms of viral respiratory infection are mediated, at least in part, by the host inflammatory responses (10). It is not clear that enhancement of the host response would be expected to have a beneficial effect on symptom severity. Reports of immunosuppressive activity associated with some constituents of echinacea may be more promising with regard to providing a potential mechanism of action (11–13). Unless an active constituent or combination of constituents can be identified or a desired biological activity defined, we cannot address such fundamental issues as dosing, bioavailability, or pharmacokinetics. In the absence of this information, it is difficult to generalize the results of any individual study beyond the specific conditions under which the study was conducted.

Despite these difficulties, the evaluation of echinacea as a treatment for the common cold remains a valid subject for clinical investigation. The common cold is a mild and self-limited illness, but its complications—otitis media, sinusitis, and exacerbations of reactive airway disease—are important medical problems. Treatments that might prevent these complications are of obvious importance. Efforts to identify effective treatments for the common cold have met with limited success, and no treatments have been shown to prevent medically important complications. Given the need for effective therapies, it is difficult to ignore the widespread use of echinacea and the persistence of the anecdotal reports of benefit. As efforts to evaluate this remedy proceed, future studies must incorporate a careful characterization of the phytochemical profile of the study material and an assessment of the effects of treatment on the pathophysiologic processes associated with viral respiratory illness. Although echinacea is characterized as an "alternative" medicine, the usual standards of scientific evidence should be met before its efficacy is accepted by the medical community.

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ON BEING A DOCTOR

The Healing Touch

Mr. B. was lying on the hard, flat ER cot when I pulled back the curtain surrounding his bed. It was 5:00 a.m., and he was sleeping quietly. Given the hour, I felt a twinge of guilt at waking him up for questioning and examination, so I stared at him for a few seconds. His face was gaunt and his full head of hair a stark white. I glanced down at the triage report sheet—he was an 86-year-old male coming in with fatigue. I noticed that his legs were hanging over the edge of the cot and realized that he must be well over 6 feet tall.

I took a deep breath and walked toward his bed. My moment of hesitation stemmed from more than simply not wanting to disturb his tranquil sleep. I was nearing the end of my second straight week of 14-hour-with-no-break night shifts as the lone internist consultant in the ER. Among my fellow residents, this is recognized as a valid learning experience but a dreaded one because of the hours and never-ending flow of work. At this time of day, with my circadian rhythm strongly enticing me to sleep, I was nauseated and cold from fatigue, and the fascinating nature of my work was far from my thoughts.

I had Mr. B. categorized in a split second: He is going to be from a nursing home. He is going to be demented. He will not be able to give me any history.

"Mr. B., sorry to wake you," I said softly. He did not wake up. "Mr. B.. . ." I said, touching his shoulder.

He awoke, looked at me, and, before I could introduce myself, said, "Thanks for coming, nurse, I'm very thirsty. Could you get me some water?"

Deep breath in and out. OK, good. Don't overreact because you're tired. This has happened countless times before.

"Actually, Mr. B., I'm the *doctor* that is going to see you. Here is some water," I replied, handing him a cup of tap water.

After a few sips that were followed by a fit of coughing, he placed the cup on the side of the bed and looked at me expectantly. I started asking him questions about the nature of his symptoms, his medical history, and so on. Perhaps *firing* the questions would be a more appropriate term, as I was acutely aware that I had many patients still waiting. At least, this is how I justified my rushed, closed-ended questioning to myself.

Mr. B. answered me painfully slowly and hesitantly. He said he did not want to give me incorrect or imprecise answers. It was difficult to keep him focused, as he would constantly go off on tangents. He did not want me to call his wife at their home either, as she would surely be asleep, and any call at this hour would make her panic and think that something was terribly wrong with him. (What? He still lived at home with his wife? Oh yes, they still took daily walks together to buy their bagels for lunch. Please let me be so lucky at his age!)

The history was vague and inconclusive. No matter; quickly on to the physical exam. Vital signs were normal, as was the head and neck exam. I then exposed his frail, thin chest for the cardiac exam.

"I'm sorry, Mr. B., my hands are cold," I warned him.

"Please do whatever you have to, doctor, it won't bother me," he answered serenely.

I rubbed my hands together, to no avail, and then placed my right palm on his parasternal area to feel for a heave. Mr. B. did not flinch when my frigid hand touched his skin. My other hand gripped the railing at the side of the bed. Mr. B.'s arms then started slowly moving toward my body. I thought he might attempt to play with my long hair, as some of my older but to date exclusively female patients have done in the past. Fine, I thought, it will distract him while I complete the exam.

Instead of my hair, he reached out to grasp my resting hand. Then, suddenly, this man, who had until now spoken and moved so very slowly, started rapidly and vigorously rubbing my hand between both of his.

I stopped my exam to stare at what he was doing.

"To warm up you up, doctor. My wife also gets cold when she's tired. This has always helped her," Mr. B. explained, never taking his eyes off his task. "You should be sleeping to take care of yourself instead of old men like me," he added.

When he finished rubbing one hand, he proceeded to do the same to the other. It felt incredibly good, and I continued to watch silently with amazement. He was the sick one, not me. And yet this man, with whom I had been impatient for the past 20 minutes, was concerned about my well-being! My impatience and haste dissipated; I was truly touched by his act of kindness and his words of selflessness. It is impossible to convey the feeling of goodness that Mr. B. gave me that morning, but at that moment, it was clearly the patient rather than the doctor who had the healing touch.

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ON BEING A PATIENT

Trust

How'd you miss that frog, Doc?" There was a tinge of irritation in Ezra's voice.

No use making an excuse. I steadied my balance, planting both feet astride the flat-bottomed boat and squeezed my eyes shut to stop the stinging. Sweat ran over my brow, down my cheeks and into the corners of my mouth. It had a bitter, coppery taste from the headlamp.

"That's awright. Don't worry about it. I'll put you on another one."

Ezra could be a demanding teacher, but he was also practical. Razzing me wasn't going to put more frogs in the boat. There were half a dozen in a burlap bag behind me. In spite of countless forays hunting and fishing together in the marsh, frogging was new to me.

I opened my eyes and replanted my feet in anticipation of our moving. He eased his paddle over the side of the boat and pushed us forward out of the thick algae and grass.

"Let's go over there. Should be some frogs in those lily pads, Doc."

A click followed by the soft electric purr of the trolling motor, and Ezra maneuvered us into open water. The din of insect sounds subsided as our movement created a little artificial breeze. By then I had stopped thinking about the mosquitoes. I stood over the front of the boat holding a 10-foot pole tipped with a spring-action gig, concentrating on keeping my balance and looking for the reflection of frog eyes in my headlight.

The nighttime marsh was alternately black and silver. Overhead, little patches of spring sky shone, and occasionally the moon could be seen peeping through heavy clouds. It might rain. My headlight swept ahead 20 or 30 feet. I looked over the side of the boat and let my lamp beam penetrate the tea-colored water. Except for a brown-green glow, I saw nothing.

"Keep your head inside the boat, Doc. We run over an alligator and start' it, it could lash its tail gittin' outta the way an' take your head off. I seen a guy get his neck broke that way."

Something to remember. I redirected my light beam ahead of the boat looking for the white reflection of frog eyes. Snake and turtle eyes were different. I looked out for alligator eyes too.

I was struck by the irony of this doctor–patient relationship. In the office our relationship was somewhat conventional; he was deferential and treated my expertise with a bit of awe. He was the heart patient and I was his doctor. The marsh was different. Here Ezra and I were in each other's hands. The field was more nearly level. I was the greenhorn who needed his expertise to get in and out of the marsh in one piece. I enjoyed his friendship, but I also valued entering an inaccessible wilderness with a master guide. He liked the companionship, but also the reassurance that his doctor was with him and could pull him out of the marsh if need be. I felt a twinkling insight into the patient's predicament—trusting a doctor to get through a dangerous stretch. What was the basis for that trust?

A year earlier, Ezra was hauled out of the marsh in congestive heart failure; a hunting buddy dragged him (reluctantly) to my office on the advice of my senior partner, also on the hunt. Ezra was small and wiry. Used to hard work, he figured his breathlessness was nothing more than "flu." I examined him and told him what I thought was wrong. He registered surprise, but not doubt. Later, as I got to know him, this relatively early trust puzzled me, because I learned just how deeply he distrusted authority. A lot of this stemmed from his real-life experience with overconfident doctors, lawyers, and judges he guided in the marsh. Yet for some reason, he chose to trust me early in our relationship. What accounted for this? Perhaps it was transference of trust from my senior partner, Joe, to me. Was it self-confidence, confidence that he could tell if something I told him didn't sound right? I don't think it was necessarily my wordy explanations of his problems. He told me, "Don't worry about explaining everything. You jus' get me outta this and I'll stick to you like glue." Maybe it wasn't completely rational—something more akin to personal chemistry.

I scanned ahead of the boat for frog eyes and alligator eyes. To my right and left, I saw wide-space amber reflections like little periscopes just visible above the water's surface.

"Doc, we're getting hung up in this algae. You're gonna need to get out and pull us through this."

Surprisingly, my first reaction wasn't to question the logic of getting out of the boat and wading through an alligator-infested marsh. Perhaps my predicament was a bit like the resignation a patient with no good alternative feels when a surgeon diagrams his or her outlandish plan on their abdomen. What were the options? I knew the bottom was too soft to push off with our gig-poles, and I couldn't think of a better idea. I was resigned to our predicament. Moreover, Ezra was just eminently trustworthy to me. Of course I had plenty of reason to trust him—we were close friends by now, and during our many excursions into the marsh he had never steered us wrong. Still, I couldn't help wondering: Was he an alligator expert? He knew this would be safe? I put down my gig, removed the headlight and battery, and readjusted the shoulder straps to my waders.

"What'll the alligators do when I wade ahead?"

"They'll move away. Don't worry about 'em. Keep both hands on that rope tied to the front of the boat. If you step in a hole, your waders'll be fulla water an' sink you like lead. You'll need the rope to pull yourself up."

"You mean an alligator hole?"

"Yeah."

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These were 20 feet in diameter and might be 7 or more feet deep this time of year, wallowed out during the dry season. I was glad he pointed this out. It would have been easy enough to drown with waders full of water, and Ezra, with his weak heart, probably wouldn't have been able to pull me out.

I lowered myself over the boat's edge, boots sinking into the mud and waders immediately filling with water. I pulled myself through the mud and around to the front of the boat. Grabbing the nylon rope, I started slowly tugging us forward out of the grass and algae and into open water. Being out in front of the boat felt eerily like going under the knife. I felt a strong urge to focus on trusting Ezra. Without my lamp, I couldn't see light reflecting from the alligators' eyes, but at the surface level I could see the small black silhouettes of their foreheads disappear. Little eddies appeared where their eyes had been.

Without warning, my head slipped under the water; I can only liken the sensation to the moment before anesthesia works, when you give in to trusting that you'll come out on the other side of the experience alive. After a split second of disorientation, I realized that I had stepped over the edge of a hole. My waders, already filled with water, pulled me down a slimy embankment. In total blackness, I focused on not letting the rope slip out of my hands. A thought flashed through my mind: He says the alligators are gone; I'm sure he's right; my legs are intact. I reached the bottom of the hole and began to pull the rope hand over hand until the rope was vertical and the boat directly overhead. I pulled myself out of the water and grabbed the bow. I wiped my eyes. Ezra was leaning over the edge, his headlamp on, looking at me; the surgeon was going to tell me that I was still in one piece.

"Hey, Doc, you awright?"

"Yeah. I think we're clear of the grass now, you can use the motor."

I was glad that was over and climbed into the boat.

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Cockroach

She carried them across the continent
securely stacked in a car's back seat,
in a dozen cartons *This Side Up*,
their plastic trays lined in newspapers
moist enough to last for several weeks,
a near eternity for roaches. This is
much more than I want to know about them
but, after all, she's sick, so I listen—

her interest first perked when visiting
a *luxury apartment* in Barbados
where she noticed the bugs were not only
more speckled and slower than the ones
she grew up with, but big enough to use
in her experiments. Forty years later
she knows more about roaches than anyone
in the world, but now she's leaving it.

The pheromes that link them together
have made her famous. In the world of roaches
communication almost never breaks down.
She's built her life around their carapace
of virtue—their crisp integrity,
their scuttering quickness, their steadfast pursuit
of a dark place. They'll long outlast us,
she remarks. I have no fears. And no regrets.

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LETTERS

COMMENTS AND RESPONSES

Reporting Enrollment in Clinical Trials

TO THE EDITOR: Gross and colleagues (1) point out that failure to report the quantitative details of the recruitment process and to provide qualitative descriptions of the population being recruited limit the generalizability of randomized, controlled trials (RCTs). Although more thorough reporting would certainly help identify trials with potentially limited generalizability, it would not help clinicians apply trial results to individual patients.

To enhance the applicability of RCTs, investigators must obtain patient-level data on those who choose not to participate. Methods to do this have been proposed (2, 3). Only by understanding the precise types of patients lost during the recruitment process can investigators determine how selective enrollment may alter the observed relative and absolute efficacy of the intervention being studied (3). Understanding which patients are selectively lost during recruitment may also help future investigators limit such problems by targeting these difficult-to-enroll groups.

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TO THE EDITOR: Gross and colleagues (1) seem to have overlooked some issues involved in the performance of a clinical study. Study recruitment involves many methods and often many people. Several of my patients have indicated that they would never enter a research study, hence they are never asked. Are they eligible decliners or not? An eligible patient may agree to participate but then find that his caretaker cannot bring him to the extra required visits. Responders to an advertisement may be potentially eligible but decline because of the number of visits required, because of time constraints, or before eligibility can be confirmed. They may be eligible and interested but discouraged from participating because the research staff finds them unreliable. On a day when I am very busy, I might not recruit an eligible patient to whom I would otherwise spend a lot of time explaining the rationale and importance of the study. Should I count that patient as eligible or not? And if I didn't have time to recruit the patient, how am I to find the time to document this? Keeping track of these types of cases and accurately classifying them are no small tasks. Researchers often don't have time to do them and, when they do, may not be reimbursed for it.

When a reader interprets the results of a study, the principle of caveat emptor always applies to generalizability. Requiring a description of how many participants are screened adds a layer of relatively useless data no better, I suspect, than myriad other factors that could be used. More important would be a description of the differences between patients who attend the clinic where the researchers are recruiting and those attending another clinic. (By the way, I am the first author of an article [2] that Gross and colleagues most likely cited as deficient.)

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TO THE EDITOR: Although Gross and colleagues' study (1) was itself a cross-sectional review, it was excellent to see that the authors provided enough information to calculate the recruitment fraction in their own work. If we consider the RCTs they found eligible for study ($n = 172$) divided by the potential number identified ($n = 215$), their eligibility fraction is 0.80. If we then consider the number of RCTs that reported adequate data for analysis ($n = 81$) as "enrolled," Gross and colleagues' enrollment fraction is 81 divided by 172, or 0.47. Finally, their recruitment fraction would be 0.47 multiplied by 0.80, or 0.38. Thus, 2.7 RCTs were screened for each enrolled.

On the other hand, it seems that the authors' equation for determining the recruitment fraction is missing an important component. The authors explain that getting from a target population to a pool of potential participants involves engaging a subgroup of that population that can be practically and ethically studied. We can consider these potential participants the ***engagement fraction.*** The authors imply that, unlike the eligibility or enrollment fraction, this fraction cannot be easily described with quantitative data and is thus left out as a multiplicand. This grossly overestimates recruitment success.

Using Gross and colleagues' article as an example, we can presume that the target population was all RCTs published in important journals between April 1999 and April 2000, with a practical subgroup of those in *Annals*, *The Lancet*, *JAMA*, and *The New England Journal of Medicine*. If we define important journals as those indexed by MEDLINE, we find that 11 539 trials in humans with RCT given as their publication type were published during this period. Gross and colleagues' engagement fraction is thus 215 divided by 11 539, or 0.02. Their true recruitment fraction is then 0.007, and 142 RCTs would have to be screened for each one enrolled.

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Reference

1. Gross CP, Mallory R, Heiat A, Krumholz HM. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? Ann Intern Med. 2002;137:10-6. [PMID: 12093240]

IN RESPONSE: Halpern emphasizes that both qualitative and quantitative information on the enrollment process is needed to help clinicians apply trial results to individual patients. We strongly agree. Detailed clinical information about patients who were eligible but elected not to participate could yield important information about the degree of selective enrollment and the impact of this selectivity on applicability. As we mentioned in our article, however, it is not always possible for investigators in large multicenter trials to gather this information. Further developments that can facilitate these activities will be of great benefit.

Friedman raises the important issue of the lack of consensus about the definition of eligible versus screened patients. Although the original CONSORT (Consolidated Standards of Reporting Trials) statement specifically included the number of "eligible" patients in the flow diagram, no specific definition was provided (1). The revised CONSORT statement clarified matters somewhat; this flow diagram begins one step earlier in the enrollment process, with the number of patients "assessed for eligibility" (2). We used a similar framework for our analysis, which presumes that if patients are never approached, they would not be included in the initial "assessed for eligibility" portion of the diagram. Of note, a recent report found that only half of published randomized trials included a flow diagram and that inclusion of such a diagram was associated with improved quality of reporting (3). Since a lack of clarity about which information is pertinent to include in the diagram may have been one of the factors that hinders reporting, further efforts to clarify and standardize the enrollment terminology may be warranted.

Abel raises the issue of the engagement fraction, which he defines as the proportion of the full target population that was engaged by investigators as potential participants. He uses the MEDLINE database as a sample of the full target population for our study. Although we agree that this quantitative information would be very useful, in the vast majority of clinical syndromes, the true size and characteristics of the full target population (the denominator) are unknown. Furthermore, collapsing the concept of recruitment, which begins at the point of investigator–patient contact, with engagement, which describes the way in which investigators contact potential participants, does a disservice to the distinct and important information that each term provides.

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The Risk–Benefit Profile of Commonly Used Herbal Therapies

TO THE EDITOR: I commend Edzard Ernst on an excellent comprehensive review of several popular herbs (1). However, I noticed that he did not mention a relatively recent randomized, controlled trial of St. John's wort in 200 outpatients with severe depression (baseline Hamilton Depression Scale score ≥ 20), which concluded that the herb was no more effective than placebo (2). In my opinion, the negative results of this large, multicenter, rigorous trial call into question the positive findings of all meta-analyses and systematic reviews showing benefit from St. John's wort in patients with depression.

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IN RESPONSE: I could not include the negative trial of St. John's wort by Shelton and colleagues (1) because it was published after I submitted my article to *Annals*. However, I do not agree that this trial, although rigorous, calls into question the results of previous meta-analyses. First, one trial cannot outweigh dozens of previously published studies. Second, and more important, Shelton and colleagues examined severe depression, while the vast majority of the previous investigations included only patients with mild to moderate depression. St. John's wort may well work for one type of depression but not for the other.

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Careful Conversation about Care at the End of Life

TO THE EDITOR: Jansen and Sulmasy (1) are correct in cautioning against blind acceptance of a "double effect" ratiocination for ethically complex issues that normally surround end-of-life decision making. However, the examples offered do not support their premise that double effect can be reduced to a simple distinction between physical and existential suffering. In case one, the patient, who has already required intermittent respiratory support, may say that she fears loss of dignity, but her impending death will most likely be due to slow suffocation. The appropriate moment to begin sedation to avoid such an outcome is when the patient says the struggle to breathe has become intolerable, regardless of how she characterizes that struggle. Case 3 is equally straightforward (although problematic for the authors' purposes). The patient is not choosing death by suicide. He is choosing an alternative death to expanding intracranial pressure. This is a central theme of palliative medicine: to help people with terminal illness understand the various ways they may die of a particular illness and help them choose a plan of care that offers the most effective palliative interventions. (It should be noted, however, that assisted suicide is not a palliative intervention.) The authors present valid concerns about blanket application of interventions that carry grave moral implications without first exercising intense soul searching. (For example, I routinely obtain an ethics consultation before proceeding with palliative sedation.) However, I object to the suggestion that the current state of knowledge and therapy for existential suffering is comparable to that for physical pain when, for the former, there are no agreed-upon definitions, or proven therapeutic methods, or even instruments of measure. To argue that physical pain can be teased out of the multidimensional suffering of terminal illness and then used as sole basis for the application of appropriate palliative options, to the disregard of the whole person, is archaic mind–body dualism.

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TO THE EDITOR: I agree with Jansen and Sulmasy (1) that terminal sedation and voluntarily stopping eating and drinking are more morally complex than is usually acknowledged (2–4). In their paper, only case 2 was fully consistent with the rule of double effect because sedation was an unintended but foreseen consequence. But might not the purposeful sedation in case 1 have been intended to relieve suffering and the shortening of life only foreseen? (Furthermore, to suggest that this patient, who had severe muscle weakness, required intermittent respiratory support, and feared impending loss of dignity had disproportionately mild existential suffering seems outrageous.) Intention and proportionality are highly dependent on the intender's views, values, self-awareness, and experience and therefore have the potential for self-deception and oversimplification. Furthermore, the generalizability of the rule of double effect remains controversial in many ethical circles (5). The rule of double effect emanates from Catholic moral tradition and focuses primarily on physicians' motivations and value judgments. It is to be hoped that physicians are responsible for both "foreseen" and "intended" consequences and that patients' values, informed consent, proportionate presence of suffering, and absence of less harmful alternatives are more central to evaluating the propriety of given clinical actions (2, 5).

I agree that the "principle of collaboration" is key. Physicians' suggestions can be coercive, and they must take responsibility for participation in (as well as withdrawal from) patients' actions. Yet many patients remain painfully unaware of their end-of-life options and need expert help. To withhold information about legally permitted options when a patient is suffering intolerably and requesting assistance also seems unethical. A physician may propose alternatives, recommend against a course of action, or refuse to participate but should not leave the patient uninformed. Physicians must think through the meaning of their participation but should not forget that the patient's suffering and values remain paramount. The rule of double effect focuses attention primarily on the physician and therefore is a piece of a larger puzzle for clinicians who find it fundamental.

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TO THE EDITOR: When discussing terminal sedation (more palatably referred to as palliative sedation), Jansen and Sulmasy (1) state that the rule of double effect is morally acceptable if "one does not aim at unconsciousness directly" and "unconsciousness is not the means by which one intends to relieve symptoms." I contest this interpretation, since unconsciousness is certainly the means to relieve suffering in refractory situations. Consequently, I am perplexed by the authors' assertions about the moral and therapeutic actions of sedation. If they believe that suffering is not directly relieved by sedation, why sedate?

Jansen and Sulmasy then state that patients should not be sedated for existential suffering, even after other therapeutic interventions have been unsuccessful, because it is tantamount to "physicians . . . giving up." Their realistic concern is that many patients who are initially unresponsive to counseling respond favorably over time and that the need to treat existential suffering with sedation is not sufficient given proportionate reasoning. I understand their argument but believe they trivialize the significance of existential distress. By restricting palliative sedation to physical suffering, they disregard the anguish of existential suffering and, more important, may precipitate further suffering. That said, I argue that anyone sedated for existential distress must be in the advanced stages of a terminal illness with a documented do-not-resuscitate order, should have undergone aggressive psychological or psychiatric intervention, and should first be considered for a trial of respite sedation. In respite sedation, the patient is sedated for a limited period to assess the effect of sedation on existential suffering and the need for further sedative pharmacotherapy (2). Respite sedation may allow sleep-deprived, anxious patients to regain the ability to deal with existential issues and may thereby preclude the need for continued sedation.

Finally, the authors offer that "sedation of the imminently dying" fulfills the moral approbation of double effect but define "sedation toward death" as "rendering the patient unconscious, not to serve future consciousness but to shorten life." Such words distort the true character and purpose of palliative sedation. I hope that no physician would use sedation to knowingly and deliberately shorten life, but rather to relieve suffering. Physician intent is intimately bound to the rule of double effect. If sedation is used to shorten life and cause death, it is clearly no longer palliative sedation but euthanasia.

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Disclaimer: The opinions expressed in this letter are those of the author and do not necessarily represent the opinions of the Department of Veterans Affairs.

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IN RESPONSE: We do not believe that the rule of double effect can be reduced to the distinction between physical and existential suffering. This distinction is important in applying the proportionality clause in the rule of double effect, but the rule should not be identified with this clause. Nor do we deny that this rule is controversial or that it is sometimes difficult to apply. But like any other moral rule, neither the fact that it can be misapplied nor the fact that it has its origins in religious thought establishes it as invalid. Properly understood, the rule of double effect holds that it is wrong for a clinician to intend to make a patient permanently unconscious as a means of treating his suffering. It does not forbid risking permanent unconsciousness as an unintended side effect of treating suffering occasioned by severe symptoms, such as dyspnea. Nor does it forbid respite sedation, which is intended to reduce consciousness temporarily. A distinction between primary and secondary sedation is an interesting suggestion and deserves further discussion. However, the rule of double effect could still be used to justify benzodiazepine coma for refractory delirium, even if the drugs do not treat the underlying delirium, because the clinician is aiming to eliminate hallucinations and agitation.

The distinction between physical and existential suffering does not rest on any mind–body dualism, archaic or otherwise (1). This distinction is readily acknowledged in the treatment of nonterminal patients (2), and, increasingly, research in palliative medicine has begun to discriminate among different kinds of terminal suffering (3, 4). This research has important and insufficiently appreciated implications for the proper treatment of suffering at the end of life. In particular, there has been a tendency in the medical literature on terminal sedation to view terminal suffering as sui generis. Unlike that of other patients, the suffering of the terminally ill has all too often been presented as an undifferentiated phenomenon. We believe this to be a serious mistake.

Regarding the principle of collaboration and its application to practices such as voluntarily stopping eating and drinking, it is crucial to realize that clinicians are implicated in the decision to inform patients of this option. This means that if it is wrong for a patient to engage in this practice, then it is wrong for a physician to inform the patient of the option. Clinicians do not avoid the moral difficulties associated with voluntarily stopping eating and drinking by claiming that they merely informed the patient of the option and let him or her choose to engage in it.

It is true that terminal sedation and voluntary stopping of eating and drinking can be combined and that this may raise further ethical questions than either practice alone. However, once a patient has been sedated, a further ethical problem does not result from his incapacity to change his mind. As long as the initial decision to sedate is ethically justified (that is, it meets the conditions we defined as sedation of the imminently dying), then the withholding of food and fluids may be permissible. Clinicians are not required to take disproportionately burdensome steps to keep sedated, imminently dying patients alive.

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Note: Two additional letters related to this discussion are available at www.annals.org.

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Physician Involvement in Voluntary Stopping of Eating and Drinking

TO THE EDITOR: Jansen and Sulmasy (1) categorize as immoral our position (2) that physicians should notify dying patients who request physician-assisted suicide of their right, as an alternative, to stop eating and drinking. We agree that it is important to account for our moral intuitions, including those about morally acceptable actions for physicians caring for patients at the end of life. However, it is important not to confuse religious intuitions with moral intuitions and for physicians not to impose their personal moral or religious intuitions on patients when they know that they are not widely shared.

Physicians are not normally required to participate in actions that violate their moral or religious views. However, when they know that many people disagree with their moral views, they are required to practice "moral tolerance." But according to Jansen and Sulmasy, if physicians have a moral view that suicide is unacceptable—a view they know is not universally shared—they are morally required not to inform patients of the option to choose a course of action such as refusing food and fluids, which the physician regards as committing suicide.

This is a form of moral paternalism that almost everyone who does not confuse morality with religion would regard as unacceptable. We agree with Jansen and Sulmasy that physicians need not approve of patients' decisions to refuse food and fluids, but this does not mean that it is acceptable to withhold knowledge of patients' legally protected right to do so. Physicians may refer patients to another physician who has no moral objections to that option, but they should not impose their own religiously based moral views on patients by refusing to inform them of their legally sanctioned options.

In our article (2), which was criticized by Jansen and Sulmasy, we claimed that for dying patients, refusing food and fluids was a noncontroversial alternative to physician-assisted suicide. However, we did not mean that everyone approved of this choice. We meant that physicians must honor the refusal of food and fluids by patients who have no religious or moral views prohibiting such refusal, regardless of the physician's own personal religious or moral views. Nothing in Jansen and Sulmasy's article provides any argument against this claim.

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IN RESPONSE: The letter by Gert and colleagues begins inauspiciously. They claim mistakenly that we categorized as immoral their position that physicians should notify dying patients who request physician-assisted suicide that, as an alternative, they may stop eating and drinking. We made no such claim. As is abundantly clear from our article, we advanced a much more modest claim: that *if* a patient's voluntary refusal of food and fluids were equivalent to suicide, and *if* a clinician were to believe that this patient's suicide would be immoral, then it would be wrong for a clinician to inform the patient that he or she had a legal right to stop eating and drinking. This is part of the moral complexity that we claimed proponents of the practice of voluntary refusal of hydration and nutrition have failed to address. Gert and colleagues attempt to address this complexity by invoking the concept of moral paternalism. While we welcome careful discussion about the nature and limits of paternalism in medicine, their proposal that a physician should not withhold information if it is not universally agreed that withholding such information would be morally correct is unhelpful. If a clinician were to inform a seriously depressed but otherwise healthy patient that he has a legal right to refuse food and fluids as a means to committing suicide, then the clinician's conduct clearly would be wrong. This would remain true even if there were, as there no doubt are, some persons who think otherwise.

The real issue concerns what a patient has a moral right to know. The voluntary refusal of foods and fluids by patients who are capable of eating and drinking is not currently the standard of care in palliative medicine. For this reason, clinicians who oppose this practice do not deny their patients information they are entitled to have when they do not inform them of this option. Failure to grasp this point may have led Gert and colleagues to claim falsely that patient refusal of hydration and nutrition is a practice that avoids moral controversy altogether.

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Reflections on Medical Journals

TO THE EDITOR: Dr. Kassirer makes statements about journals that, because he has not troubled to present data, are hard to check (1). Nevertheless, we were amused by his response to "Standardization," particularly when he is attempting to determine whether progress has made medical journals better. He writes, "A small cadre of editors recently recommended that authors of original research papers standardize their content" and then pours scorn on such efforts as CONSORT (Consolidated Standards of Reporting Trials). Had he read the article he cites by Rennie (2), he would have realized that the effort sprang from a serious problem, recognized by nonscientists in the community (3); that there was extensive consultation with scientists worldwide; and that throughout, editors constituted a small minority. Their role was in implementing what the community wanted.

Kassirer derides editors for sending "manuscripts back to authors if they fail to conform," asking, "Does such copycat uniformity force science into a straitjacket and impede creativity?" CONSORT, QUOROM (The Quality of Reporting of Meta-analyses), MOOSE (Meta-analysis of Observational Studies), and STARD (Standards to Improve Reporting of Studies of Diagnostic Tests) are not about standardization or organization. A well-established standard for reporting research, IMRaD (Introduction, Methods, Results, and Discussion), already exists. CONSORT, for one, aims for transparency, regardless of the format, in the reporting of randomized trials. An editor may indeed send back a manuscript based on CONSORT if an author has, for example, inadequately reported the components of randomization. That decision, however, is based on content and not standardization, because poor randomization is associated with biased estimates of treatment effects (1–4). That is a profound scientific issue and not what Kassirer falsely paints as the whimsical leaning of editors towards standaridzation. CONSORT and the other statements were drawn up after an intense effort to discover the evidence for each recommendation. Does Kassirer object to that? Kassirer may not acknowledge data supporting CONSORT, but they exist and were referred to in Rennie's editorial (2, 5).

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IN RESPONSE: Despite these protestations, achieving transparency by checklist is simply an inadequate substitute for high-quality editing and peer review. The authors' data supporting the use of CONSORT are weak, as they acknowledge openly in the only reference they provide (1). It will take much better evidence than this to convince me that ossifying research reports with checklists and flow charts improves medical care rather than serves the requirements of evidence-based gurus in their aerial palaces of meta-analysis (2).

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Use of Antiviral Therapy in Patients with Hepatitis C

TO THE EDITOR: We read with interest the article by Falck-Ytter and colleagues (1) on antiviral treatment in patients with hepatitis C virus (HCV) infection. We care for predominantly indigent patients co-infected with HCV and HIV. Patients with HIV infection usually require medications such as antiretroviral agents and antibiotics to prevent opportunistic infections. These interact with drugs used to treat HCV infection (ribavirin and interferon) and cause cytopenia. Because HCV and HIV are transmitted parenterally, co-infected patients are often injection drug users. Like Falck-Ytter and colleagues, we hypothesized that our co-infected patients frequently had comorbid conditions that hindered HCV therapy.

Investigating this hypothesis, we retrospectively reviewed the medical records of 108 HIV-infected patients diagnosed with HCV infection between 1995 and 1997 at a public health clinic in Santa Ana, California (2). Of these patients, 10% had a psychiatric history, 17% had ongoing alcohol abuse, and 19% had evidence of active injection drug use. In addition, 6% had a hemoglobin level less than 10 g/dL and 4% had platelet counts less than 0.75×10^9 cells/L. Among the 108 patients, 81% returned for at least one follow-up appointment. Although the median duration of follow-up was 26 months, only one patient received treatment for HCV infection. Although well-controlled HIV infection is not a contraindication to HCV treatment, many co-infected patients have comorbid conditions that interfere with treatment for HCV. We agree with the authors' recommendations for better-tolerated HCV drugs, interventions for substance abuse, and support mechanisms to improve adherence. In addition, interventions such as growth factors for cytopenia, close monitoring of complete blood counts, and the use of pegylated interferon without ribavirin may allow treatment of patients with relative contraindications to therapy. To address these issues, we have initiated a co-infection clinic at our hospital where infectious disease specialists and hepatologists can work in tandem.

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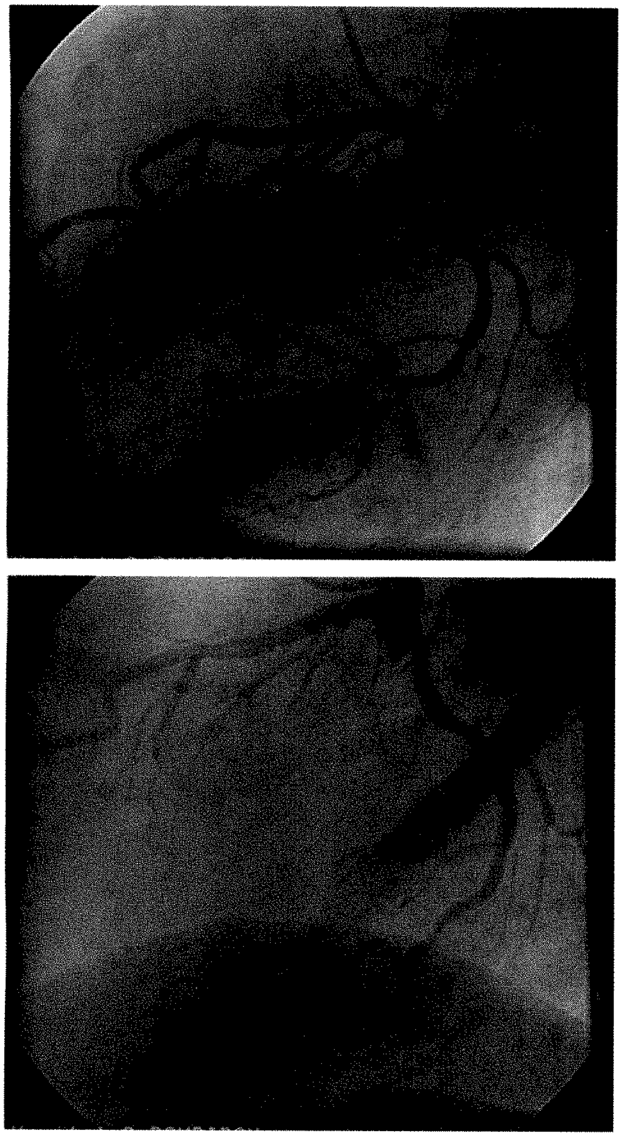
RESEARCH LETTERS

Angina Caused by Calcific Constrictive Pericarditis

TO THE EDITOR: *The Patient:* A 62-year-old man presented with retrosternal chest pain on exertion and progressive dyspnea. Results of laboratory tests were normal. Chest radiography showed cardiac enlargement and apical calcification. Two-dimensional echocardiography revealed dilated cardiopathy with anteroseptal hypokinesis without pericardial effusion or thickening. Coronary angiography showed compression of the marginal coronary artery by a calcification that induced systolic occlusion and diastolic stenosis (**Figure**, *top*). The coronary arteries showed no atherosclerotic disease and no ventricular aneurysm. Computed tomography showed basal pericardial calcification with penetration of the myocardium at the basal wall of the left ventricle.

Calcified constrictive pericarditis was diagnosed at surgery, and a radical pericardectomy was done. Multiple tight adhesions between the epicardium and pericardium were found. There were prominent calcifications over the right atria, the pulmonary artery, and the lateral wall of the left ventricle. The midportion of the marginal artery was encased by a calcification constricting the left ventricle. Histopathologic examination of the pericardium showed a nonspecific fibrocalcified pericarditis without evidence of *Mycobacterium tuberculosis hominis*, granuloma, or vascularities or eosinophils. Angiography performed 4 days after the surgery showed that a normal flow was restored in the marginal artery (**Figure**, *bottom*).

Figure. **Angiographic appearance of the marginal artery during catheterization before (*top*) and after (bottom) surgery.**



Discussion: The clinical presentation of this patient suggested ischemic heart disease. Chest pain is rarely associated with constrictive pericarditis, especially in patients without any atherosclerosis, and may cause delayed diagnosis (1–3). Although myocardial infarction and angina due to compression of a coronary artery from fibrotic adhesions has been reported (3), angina due to compression of a coronary artery by a calcification penetrating in the myocardium has not been reported with constrictive pericarditis.

The presence of pericardial calcifications suggests constrictive pericarditis in patients with symptoms of heart failure (4). In our patient, the diagnosis of constriction could be confirmed only intraoperatively. Calcified disease is common in patients with constrictive pericarditis presenting for pericardectomy; however, the incidence varies depending on the population surveyed, the cause of constrictive pericarditis, and the year of the study (5% to 76%) (4). Calcifications might be a nonspecific response to chronic inflammatory process and are positively correlated with chronic disease (4).

Constrictive pericarditis is considered idiopathic in 67% of cases (4). In our patient, we failed to find the most frequent causes (cardiovascular surgery, radiation therapy, tuberculosis, fungal disease, and chronic renal failure) (5, 6). Although medical treatment may temporarily alleviate symptoms of heart failure, patients do poorly without cardiac decortication (6).

Conclusion: Angina can be the presenting symptom of constrictive pericarditis related to a calcification coming from the pericardium and constraining a coronary artery.

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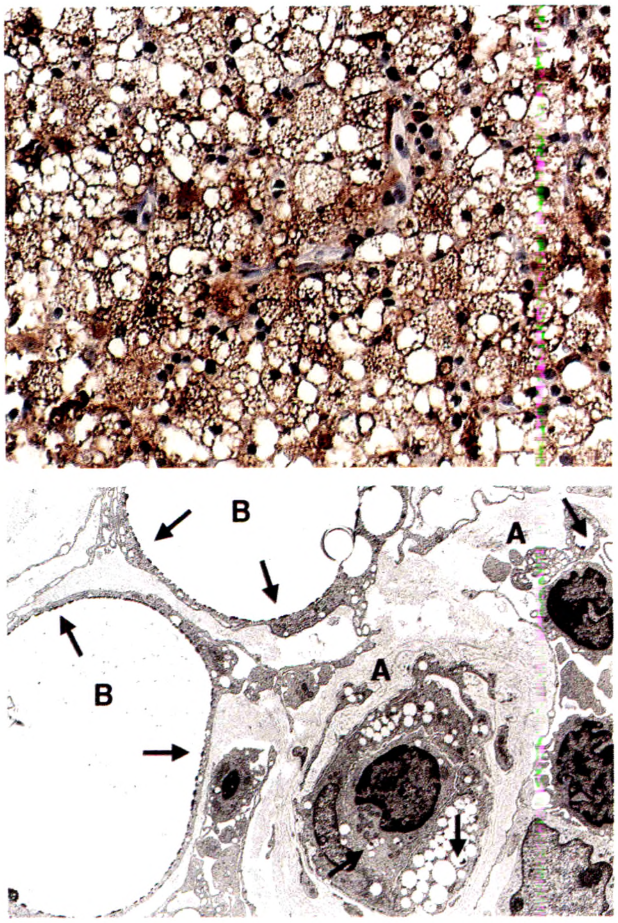
Foamy Macrophage Syndrome due to Hydroxyethyl Starch Replacement: A Severe Side Effect in Plasmapheresis

TO THE EDITOR: A 38-year-old woman had received stanozolol, cyclosporine, and frequent plasmapheresis since 1997 because of IgG λ monoclonal gammopathy with cryoglobulinemia-associated ulcerating leukocytoclastic vasculitis. Initially, gelatin-based plasma expanders and pasteurized human albumin were used. Beginning in February 1999, plasma volumes were exchanged at a 1:1 ratio with undiluted 6% hydroxyethyl starch (HES) (Fresenius–Kabi, Hamburg, Germany) because of the reported advantages of HES.

In August 2000, the patient developed severe weight loss, sensory polyneuropathy of the legs, and deteriorating eyesight. On examination, she was malnourished (body mass index, 17.6 kg/m^2) with hepatosplenomegaly and ascites. She had normocytic anemia (hemoglobin level, 7.1 mmol/L; mean corpuscular volume, 82 fL), thrombocytopenia (platelet count, 121 × 10^9 cells/L), low serum

Figure. Microscopic images.



Top. Light microscopic image of a bone marrow biopsy revealing massive infiltration with CD68+ foamy macrophages. (Hemotoxylin–eosin; original magnification, ×200.) **Bottom.** Immunoelectron microscopic image of endothelial cells with many small vacuoles (*A*) and two large vacuoles in the cytoplasm of histiocytes (*B*). The vacuoles express the characteristic peripheral amorphous material that is reactive for the anti–hydroxyethyl starch antibody (*arrows*). (Uranyl acetate and lead citrate; original magnification, ×2200.)

creatinine concentration (40 µmol/L [0.45 mg/dL]) and albumin level (26 g/L), and slightly elevated serum IgG level (15.9 g/L) and aminotransferase levels (aspartate aminotransferase level, 62 U/L; alanine aminotransferase level, 52 U/L). Magnetic resonance imaging of the brain revealed vasculitis of the choroid plexus with hydrocephalus and pituitary stalk edema. Histologic examination of bone marrow, skin, duodenal mucosa, liver, peritoneum, and dura mater and cytologic examination of the ascitic fluid revealed massive infiltration with typical foamy macrophages (**Figure**). Hematoxylin–eosin, periodic acid Schiff, and oil red O staining showed empty vacuoles. *Mycobacterium avium* infection was ruled out. Enzyme analysis excluded Wolman, Niemann–Pick, and Gaucher diseases (all lysosomal storage diseases). Immunoelectron microscopy with polyclonal rabbit anti-HES serum, performed by Dr. S. Ständer (Westfälische Wilhelm-Universität, Munster, Germany), confirmed massive tissue storage of HES, especially in the vacuoles of the macrophages (**Figure**). Although plasmapheresis with conventional expanders was continued, the patient improved only slightly. After 8 months, a bone marrow biopsy still revealed massive foamy cell infiltration.

Elimination of HES depends on distribution and back-diffusion from body tissues and metabolism (α-amylase), followed by urinary excretion (1). Persistent pruritus due to dose-dependent and time-related skin deposits has been the most frequently reported complication of HES (2, 3). Skin deposits can be detected up to 4 years after the final administration of HES (3, 4). In our patient, HES exposure (130 L within 20 months) led to symptomatic, massive, diffuse tissue infiltration with HES-laden foamy macrophages.

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GENERAL COMMENTARY

Recertification

TO THE EDITOR: At the 2002 annual meeting of the American College of Physicians–American Society of Internal Medicine, I was pleased to learn that the College will be redoubling its efforts to work with the American Board of Internal Medicine to develop an improved recertification system that will be meaningful for practicing internists and ensure lifelong professional development. As one of the many Fellows of the College who have a time-limited certificate, and one who recently recertified under the current less-than-ideal system, I believe that periodic recertification is here to stay. I also think that overall this is a good thing for our specialty. I do, however, want to suggest that the College strongly advocate for the creation of an emeritus status. This special board status would appropriately recognize the important lifelong professional accomplishment of future internists who will retire from active practice after many successful recertifications.

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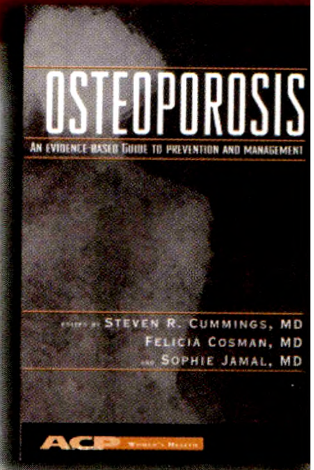
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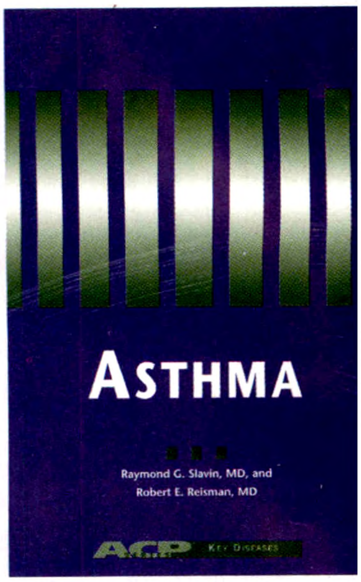

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A 45-year-old woman
esents with weight loss of
pproximately 9 kg (20 lb)
er the past 12 months. She
as been aware of no change
appetite. She eats three
eals daily and snacks most
enings[illegible] Her activity has
milarly been unchanged.
he exercises by walking 2 to
miles three or four times
eekly. She takes no medica-
on and reports no alcohol or
rug use. Review of systems
veals [illegible] 1- to 1.5-year history
a pruritic rash on the trunk
d extremities. She reports
ccasional vague abdominal
in and bloating, which sub-
de spontaneously in a few
urs, and notes the passage
flatus. She has no food
tolerance, difficulty swal-
wing[illegible]weating, tremor, con-
ipatio[illegible] diarrhea, or arthri-
s. She has normal, regular
enstrual periods and has
o to three stools per day,
ith no recent change.
The patient is 175 cm (69
) tall and weighs 50 kg (110
). Blood pressure is 115/70
m Hg[illegible]ulse is 96/min, and
mperature is 36.9 °C (98.4
). The skin shows a truncal
d proximal extremity rash
nsisting of grouped vesicles
n an erythematous base.
here is also evidence of
coriation. The remainder of
e physical examination,
clud[illegible]vic and rectal
amination, is otherwise
rma[illegible]nd stool is negative
r occult blood. The neuro-
gic examination is normal.

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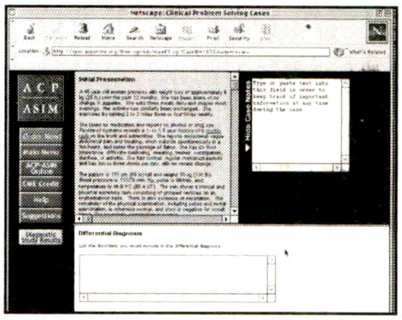

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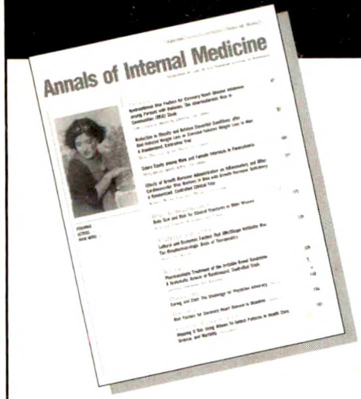

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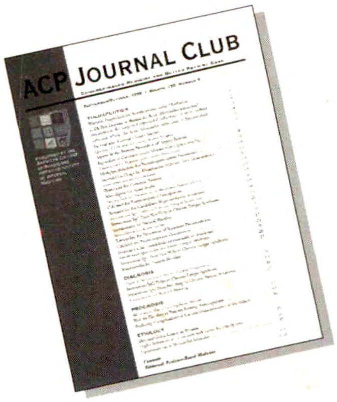

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